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TREATMENT OF ENDOMETRIOSIS AND OTHER GYNECOLOGIC CONDITIONS WITH LARGE DOSES OF ESTROGENS*

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THE use of stilbestrol in the treatment of endometriosis was described in 1948 by Karnaky[1] and Hurxthal and Arnold.[2] The purpose of this report is to relate further experience with the use of this drug in the treatment of endometriosis and in a few other conditions.

In their original communication, Hurxthal and Arnold[2] described 3 cases in which stilbestrol was tolerated with favorable results. The first patient in whom endometriosis was verified remains well and is amenorrheic after treatment for five years. Nodules cannot be palpated on pelvic examination. On several occasions, the drug has been discontinued, and painful menstruation has returned. With the daily maintenance dose of 3 or 5 mg. there have been only one or two occasions when slight vaginal bleeding occurred. The result in this case has been one of the most successful in our experience. The second patient, in whom endometriosis was also verified, was treated successfully for several years, but periodic oozing developed and the menstrual periods returned with increasing pain. An operation was performed elsewhere for what was presumed to be an endometrial tumor; however, a serous cystadenofibroma of the ovary was found, and a panhysterectomy was done by Dr. N. M. Forney, of Milltown, New Jersey. The pathological report was as follows:

> The uterus was atrophic, with a superficial fibroid approximately 2.5 cm. by 3.0 cm. A few small, intensely congested, hemorrhagic nodules were found on the posterior wall of the uterus. The cyst measured 7.5 by 6.5 cm. The endometrium showed large, irregular glands with tall columnar epithelium, and scanty stroma that was congested and hemorrhagic; the myometrium appeared atrophic. A few subserous islands of endometrium were seen. Vestiges of endometrial cysts in regressive form were present on the outer wall of the uterus.

The third patient, as reported, became pregnant while on comparatively small doses of stilbestrol, but aborted spontaneously after four months.

In addition to these 3 cases, estrogens have been administered to 25 patients in whom endometriosis was presumed or verified; to 4 patients who had uterine hemorrhages of undetermined or determined etiology; to 5 patients who had fibroids; and to 2 patients who had chronic cystic mastitis. The various drugs used were diethylstilbestrol, "micronized (des) stilbestrol,"§ dienestrol¶ and occasionally estrone sulfate. Doses varied from 5 to 50 mg. each day. In several cases testosterone propionate or testosterone cyclopentylpropionate|| has been used in conjunction with stilbestrol for conditions such as persistent oozing and malaise from the estrogen.

RESULTS

Endometriosis

There were 9 cases of histologically verified endometriosis and 16 cases in which the diagnosis was made by the usual clinical criteria. In 1 of the verified cases in which a laparotomy was performed after estrogen therapy there was evidence of scarring, but endometriosis was not found. In another case of unverified endometriosis nodules had been felt on pelvic examination, but laparotomy revealed a fibroid tumor. Whether or not endometriosis had been present in addition to the fibroid tumor and had disappeared with the institution of hormonal therapy cannot, of course, be determined.

Pain was relieved completely in 4 cases (in 2 of these endometriosis was verified), even though at times oozing of blood occurred. In 12 cases, pain was markedly decreased, and in 8 the pain was slightly decreased. In 2 patients (thirty-one and thirty-eight years of age), in spite of large doses, menstrual periods continued; since some of the periods were associated with pain, it is possible that ovulation had not been completely suppressed. In 1 patient who had marked dysmenorrhea caused by verified endometriosis, severe pain occurred in the shoulder at the time of menstruation. This was partially relieved when the patient became amenorrheic on stilbestrol therapy, and vanished

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§Micronized (des) stilbestrol furnished for a few cases by the Grant Chemical Company.
¶Dienestrol furnished by the White Company.
||Testosterone cyclopentylpropionate furnished by the Upjohn Company.

completely after subsequent panhysterectomy. This is the only case in these series in which a distant endometrial lesion was suspected.

Only 4 patients who were kept on estrogen therapy for a protracted period were without pain or menstrual periods; 3 of these had some oozing from time to time. This oozing was controlled by the injection of 100 to 200 mg. of testosterone propionate or cyclopentylpropionate. Three other patients had much less pain after a short course of stilbestrol therapy. When excessive flow occurred, the dose was increased, often to twice the preceding amount, usually with control of the bleeding.

Fibroids

Karnaky[3] states that he has seen large fibroids disappear with stilbestrol therapy. One of our patients, a forty-one-year-old woman, had uterine bleeding from a large fibroid tumor that extended up to the level of the umbilicus. Because of polycystic kidney disease and hypertension, surgical treatment was contraindicated, and she was given x-ray therapy unsuccessfully. Stilbestrol, in doses of 25 mg. a day, was then used, with immediate cessation of flow and an apparent reduction of 50 per cent in the size of the fibroid over a period of two years.

Of the 5 patients who were treated for bleeding associated with fibroids, carcinoma of the breast developed in 2; 1 patient had regular periods after cessation of nineteen months of therapy, and the other 2 were operated on. At operation on 1 of these patients, a fibroid was not found, but microscopical examination revealed chronic endometritis. The other patient was operated on because the pelvic mass, which at operation proved to be a fibroid, was increasing in size.

Menorrhagia

Excessive flowing will respond to large doses of stilbestrol.[4, 5] Karnaky[4] originally injected estrogens directly into the cervix for severe dysfunctional uterine bleeding, but he also gave these patients stilbestrol by mouth.[5] Stilbestrol, in doses of 25 to 50 mg. every one to three hours, will arrest excessive bleeding in four to six hours. This is illustrated in 1 patient of this series, a nurse, who was admitted to the hospital because of excessive flowing, presumably caused by uterine fibroids. On admission, the hemoglobin was 5.2 gm. per 100 cc.; the red-cell count was 1,600,000. She was given 1500 cc. of whole blood, which increased the hemoglobin to 7.5 gm. per 100 cc. Since excessive bleeding continued, 25 mg. of stilbestrol was given four times a day for one day, two times on the second day and once on the third day. Bleeding stopped in forty-eight hours. After three days of therapy, during which the patient received a total of 175 mg. of stilbestrol, the hemoglobin had risen to 13 gm. per 100 cc. Three more transfusions (500 cc. each) were given, and the hemoglobin remained at 13 gm. A supracervical hysterectomy revealed several large fibroids.

The withdrawal or the decrease in dosage of stilbestrol may be accompanied by profuse bleeding; a resumption of the previous dosage or an increase usually checks the flow. If bleeding is severe, stilbestrol may be administered every few hours until bleeding has ceased. One or more injections of testosterone propionate in doses of 100 or 200 mg. may also be helpful. Intravenous administration of estrogen is now being employed[6] to effect rapid termination of the flow. Amenorrhea may be produced by the regular injection of testosterone in cases in which temporary therapy is necessary. In such cases, the dosage may vary from 25 to 50 mg. three times a week or even 200 mg. a week if testosterone cyclopentylpropionate is used. When oozing or more profuse bleeding occurs during the course of stilbestrol therapy, Karnaky[4] advises dilatation and curettage, which he performs in the office with a Randall or Novak curette. In 1 of our cases in which pain and excessive flowing were caused by unverified endometriosis of four years' duration, profuse bleeding developed two years after the patient became amenorrheic on stilbestrol therapy. The bleeding could not be controlled on large doses of stilbestrol or testosterone. After the dilatation and curettage, all hormonal therapy was discontinued, and the patient had normal, regular and painless periods for six months. Subsequently, there was a gradual return of pain and excessive flowing.

In summary, of the 4 patients treated because of menorrhagia, 1 is still on therapy (over two years), and another had dilatation and curettage and is now having normal periods; in a third patient x-ray therapy to the ovaries was given since she was approaching the menopause. The fourth patient stopped estrogen therapy of her own accord after six months. One year after cessation of therapy, hysterectomy was done.

Chronic Cystic Mastitis

In spite of the occurrence of swollen or tender breasts when stilbestrol is used, we have noted almost complete disappearance of the painful nodules in chronic cystic mastitis. Stilbestrol was given to 2 patients — 1 for three months, and the other for nineteen months — in a maintenance dosage of 25 mg. of stilbestrol and 40 mg. of dienestrol, respectively. Both were completely relieved of pain. In 1 case the nodules, which were still present after three months of therapy with 20 mg. of dienestrol, disappeared after nine months of 40 mg. a day. At the completion of therapy, nodules could not be felt.

Pregnancy

Two patients became pregnant while they were on stilbestrol therapy. In 1, pregnancy occurred two

months after the cessation of stilbestrol therapy, but the other patient became pregnant during stilbestrol therapy. Of 20 patients who had clinical endometriosis (not included in this series) and who were studied in this clinic because of sterility, 5 became pregnant while on large doses of stilbestrol.

Libido

Libido was increased in 6 patients; dyspareunia was relieved in all patients with endometriosis as long as they continued to take stilbestrol.

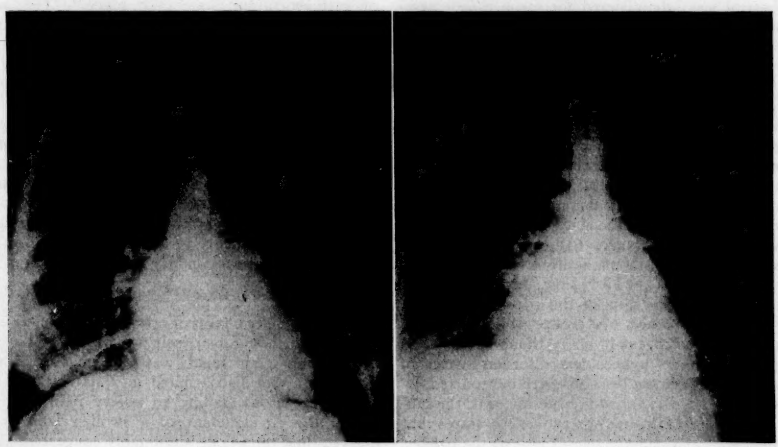
Side Effects and Complications

There is no way of predicting the patient's tolerance to stilbestrol. About 50 per cent of the women who take stilbestrol become nauseated, especially during the first two weeks of therapy. In some cases the nausea then disappears and is replaced by a sense of well-being. A few patients may continue to feel nauseated in spite of the relief of symptoms for which the estrogens were originally prescribed. The simultaneous use of testosterone did not counteract this unpleasant side effect, nor did the measures advocated by Karnaky[7] appear to be of benefit, although they were not given a critical and thorough trial.

Other complications or side effects of stilbestrol therapy have been the generalized sensation of bloating, dependent edema, edema of the labia, swelling, pigmentation and soreness of the breasts, psychosis and pulmonary congestion. The last-mentioned complication occurred in a twenty-nine-year-old woman who had rheumatic heart disease, mitral stenosis and a regular cardiac rhythm. After she had been on estrogen therapy for three months, dyspnea and orthopnea developed, disappearing a few days after the drug had been withdrawn (Fig. 1).

Another serious complication occurred in a thirty-four-year-old woman who had been given stilbestrol for unverified endometriosis. After she had received 25 mg. daily for a month, severe headaches, marked irritability, alcoholism and homicidal tendencies developed. During this time, the patient had one day of bleeding without pain. When the treatment was discontinued, the headaches and mental symptoms disappeared, but painful menstruation returned.

Carcinoma of the breast occurred in 2 patients; 1 was a diabetic patient who had been treated for menorrhagia, resulting from or associated with a fibroid tumor. The patient had taken 5 to 20 mg. of stilbestrol or dienestrol for ten months. At operation, carcinoma simplex with metastases to three axillary lymph nodes was found. To date, there has been no evidence of metastases since the radical



A B

FIGURE 1. *Roentgenograms in a Patient Receiving Stilbestrol.*
A = *Mitral stenosis before institution of stilbestrol therapy (courtesy of Dr. Max Ritvo).* B = *Pulmonary congestion (associated with dyspnea and orthopnea), which developed when the patient received 25 mg. of stilbestrol daily for three months. All clinical signs and symptoms disappeared a few days after cessation of stilbestrol therapy.*

mastectomy in June, 1949. Several observers reported having palpated a fibroid tumor (approximately 6 by 8 cm.) in this patient before estrogen therapy. When a hysterectomy was performed elsewhere, twelve months after cessation of estrogen therapy, a small leiomyoma about 1.3 cm. in diameter was found on the external uterine surface, and a small subserous endometrioma of the uterus about 1.0 cm. in diameter was found close to the endometrium. Of some interest was the patient's observation that the insulin requirement, during stilbestrol therapy, decreased from 50 to 60 units of protamine zinc insulin a day to 15 units a day. This patient treated her diabetes haphazardly, so that the reliability of this observation can be questioned.

The second carcinoma of the breast was discovered in a forty-nine-year-old woman to whom stilbestrol was administered for menorrhagia associated with menopause. A pelvic examination, under anesthesia, also revealed the presence of a uterine fibroid. This patient was believed to have chronic cystic mastitis, which had been found five years previously on examination at another institution. After three years of dienestrol or stilbestrol therapy (5 to 25 mg. a day) on which the patient remained amenorrheic and in good health generally, a growing lump appeared in the breast, proving to be malignant at operation. X-ray therapy was subsequently given successfully for excessive flowing.

Neither of these patients had a family history of cancer. A brief survey of the literature[9-10] revealed relatively few cases in which cancer developed during estrogen therapy in spite of the widespread use of estrogens in the cancer age group. With the use of large doses of estrogens in many thousands of cases of pregnancy and gynecologic disorders, cases of breast cancer have not been observed or reported.[11-13]

Nathanson,[14] who has admirably reviewed the subject of steroid treatment of breast cancer, states that estrogens may accelerate the growth of the cancer, especially in premenopausal women. Cancer may develop in the opposite breast of women treated with estrogens, but it is always difficult to determine whether this is secondary to the original growth. The percentage of such an occurrence, to date, may be no greater than that in surgically treated cases; however, estrogens are used to a great extent in patients who have inoperable or metastatic lesions.

Bilateral cancer of the breast has been reported in several male patients who were receiving stilbestrol for prostatic cancer.[15-19] According to some observers,[18, 19] these new growths are metastatic lesions from prostatic cancer, although the problem may not as yet be settled.[20]

Other Effects

Pigmentation of the nipples was noted in 4 patients (blondes as well as brunettes). This pigmentation receded slowly when estrogen therapy was discontinued.

Mechanism of Action

Large doses of stilbestrol, through inhibition of the pituitary gonadotrophins, can cause ovarian atrophy. It is logical to assume that fibroids and endometrial or breast lesions (malignant or benign) also are dependent upon or receive their growth stimulus from functioning ovarian glands. Hence, a decrease in size of such neoplasms might follow estrogen-induced ovarian atrophy, provided the estrogens or their metabolic end products do not act on the myometrium, endometrium or breast in a manner similar to that of the hormones of the human ovary. Stilbestrol causes estrogenization of the vaginal epithelium in most cases, but during prolonged use a marked decrease in the initial degree of estrogenization may take place.[21] The same phenomena undoubtedly occur in other target organs.[22, 23]

The relief of pain in endometriosis may be the result of inhibition of ovulation and the lack of progesterone secretion. Against this hypothesis is the known occurrence of pregnancy during amenorrhea induced by stilbestrol therapy. It is probable that some reaction other than simple depression of pituitary gonadotrophins is provoked by estrogen or androgen therapy in these cases. The part played by the adrenal cortex must be considered, because of the known influence of adrenal hormones on the gonads and on the secondary sex organs.

Summary and Conclusions

Relatively large doses of estrogens were used in 25 cases in which endometriosis was presumed or verified. Temporary relief was obtained in many. Treatment was discontinued in 7 patients for the following reasons: failure to relieve pain in 4 patients, the development of a swollen labia in 1, marked fluid retention, presumably congestive heart failure, in another, and psychotic symptoms that necessitated withdrawal of the drug in a third patient.

Stilbestrol therapy was used and satisfactory results were obtained in 8 cases of menorrhagia with or without fibroids and in 2 cases of chronic cystic mastitis.

Stilbestrol may be helpful in the treatment of endometriosis, but its usefulness is limited because of unpleasant side effects or undesirable complications. In a few cases, the results of treatment are most satisfactory.

It is not believed that cancer of the breast is caused by stilbestrol, but if a carcinoma is present in subclinical size, the growth may in some cases be accelerated.

Stilbestrol or other estrogens are useful in the temporary management of excessive uterine bleeding, but probably should not be employed for an

extended time in any case in which a definite family history of carcinoma has been obtained.

The nodules of chronic cystic mastitis and uterine fibroids may decrease in size, but this observation must be substantiated by further clinical observations.

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ACRODYNIA FOLLOWING INGESTION OF MERCURIAL OINTMENT*

Late Dental Sequelae

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IN THE comprehensive survey of allergy to drugs by Carr,[1] reactions to mercurial compounds are only briefly mentioned. Recent reports[2] have indicated a relation between the clinical syndrome of acrodynia and exposure to mercury or its compounds. Sources of mercury have included teething powders, mercurial ointments applied externally, mercury bichloride diaper rinses and calomel compounds used in the treatment of intestinal parasites. Recently, Bancroft, Grant and Tanner[3] reported the occurrence of acrodynia following the ingestion of ammoniated mercury ointment. The 2 cases reported below represent additional examples of the development of acrodynia following exposure to mercury through ingestion of ammoniated mercury ointment. One patient also demonstrates late dental sequelae to the disease.

Case Reports

CASE 1.§ S. C. was admitted to the New Haven Hospital on November 10, 1939, with the chief complaint of pruritus of 4 months' and abdominal pain of 3 weeks' duration. The family history was noncontributory, and the past history was considered irrelevant as elicited at that time. The child had always been in good health until June, 1939, when she was 2 years and 4 months of age. At that time, she had impetigo, which responded promptly to treatment. Two weeks after recovery, blisters developed on both hands; the blisters disappeared rapidly but within 1 week recurred and became progressively worse. The patient gradually became irritable, weak and anorexic. She avoided light and was observed to lie for long periods on her abdomen with her face in a pillow. Approximately 1 month before admission she began to pull out her hair, bleeding from the gums was noted and several deciduous teeth fell out. She scratched herself constantly; despite sedation she slept very little at night. Treatment at home consisted of oral and parenteral administra-

FIGURE 1. *Vaccinia-like Scars on the Skin of the Lower Jaw in Case 1, Seven Years after Severe Acrodynia.*

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§Reported through the courtesy of Dr. Grover F. Powers, New Haven Connecticut.

tion of vitamins A, B, C and D; liver extract; ultraviolet light; and many types of sedation, including codeine and morphine. The child was brought to the hospital because the progressive severity of the disease suggested an impending unfavorable outcome.

Physical examination demonstrated characteristic signs of severe acrodynia. The fingers were reddened, swollen and damp. The palms and soles were peeling, and desquamation was observed elsewhere — on the hands and feet, the arms, the legs, the lower portions of the trunk, the buttocks and the vulva. Patchy thickening of the skin and erythema associated with vesiculation and crust formation were noted in the latter areas. Multiple ulcers were present in the mouth, and at one time it was feared that the lower jaw might slough. Irritability was marked. The temperature was 37.2°C. (99°F.), and the blood pressure was 120/80. Laboratory studies, including routine chemical analyses of the blood, were not remarkable.

FIGURE 2. *Partial Edentia Seven Years after Severe Acrodynia in Case 1.*

Note the scars on the right hand at the base of the ring finger. Similar scars were present on several toes.

The child was treated supportively; she received several blood transfusions and gradually began to improve. She was discharged after 2 months in the hospital, still somewhat irritable and still having some hypertension and some redness and peeling of the hands, but with evidence of healing of the mouth lesions and with no new ulcers.

She was seen subsequently in 1946 at Babies Hospital, New York City, by one of us (F. N. S.) while under investigation for an unrelated illness. It was interesting to observe that sequelae to the severe acrodynia were present in the form of vaccination-like scars on the lower jaw, hands and feet (Fig. 1 and 2). Seven of the permanent teeth of the mandible had failed to erupt. The mother stated that the child showed progressive recovery from the acute disease after discharge from the hospital in 1939, and was well except for the scars approximately 6 months after discharge and 1 year after the illness had begun.

In 1949 (10 years after the original disease) the mother was questioned by mail concerning exposure to mercury. She replied that prior to the acrodynia, the patient had had four or five spots of impetigo, which had been treated with ammoniated mercury ointment. Also, she had got hold of a tube from the bathroom shelf, and the mother feared that she had eaten some of the ointment. Communication with the patient's orthodontist disclosed that the four lower incisors, the right lower cuspid, and the right lower bicuspids had failed to develop, presumably because of destruction of their dental follicles when the mouth lesions were severe. The alveolar ridge in this area was atrophic (Fig. 3 and 4). Because eruption of a full complement of teeth in the upper jaw produced a dental imbalance, the upper first bicuspids were removed, and a denture was supplied for the lower jaw. An excellent functional and cosmetic result was thereby achieved.

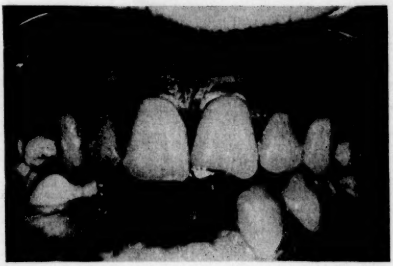

FIGURE 3. *Condition of the Teeth Twelve Years after Severe Acrodynia in Case 1 (Courtesy of Dr. Joseph D. Eby, of New York).*

All lower incisors, the lower right cuspid and the lower right bicuspids have failed to erupt. The upper first bicuspid has been extracted on each side to balance the slightly underdeveloped mandible.

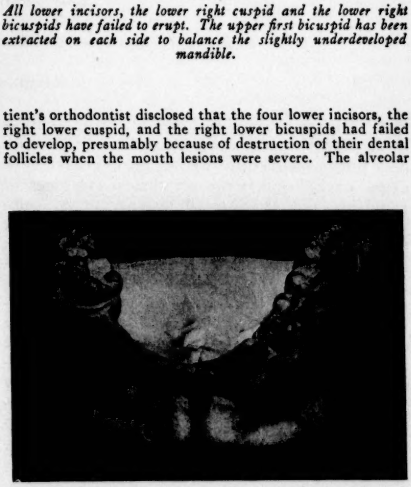

FIGURE 4. *Dental Cast of the Lower Jaw Twelve Years after Severe Acrodynia in Case 1 (Courtesy of Dr. Joseph D. Eby, of New York).*

Note the marked atrophy of the alveolar ridge, where permanent dental structures had been destroyed during the active phase of the disease.

The patient was examined by Dr. Robert W. Nespor, of Westport, Connecticut, on June 21, 1952, who reported that at the age of 15 years, she weighed 105½ lbs., and was 62½ inches tall. She appeared to be in excellent health. The blood pressure, determined in the sitting position with the mercurial sphygmomanometer, was 90/50 on two successive occasions. The pulse rate was 72 and regular. The heart sounds were of good quality.

Case 2. S. B., a 2½-year-old boy, was admitted to the Children's Hospital of Cincinnati on April 27, 1951. Eight weeks prior to admission he had had an upper respiratory infection, treated with penicillin and sulfadiazine. His twin sister suffered from a similar infection and was treated in the same manner. After 2 weeks the sister improved, but the boy seemed irritable with prolonged crying spells, and refusal to eat. He would not go outdoors; he constantly wanted his parents to hold him. He became belligerent toward his sister whereas previously he had been delighted to play with her. Three weeks before admission "pink" palms and soles, with deep-seated vesicles and some pustules, developed. He became extremely irritable and rubbed his hands and feet constantly. Anorexia and insomnia became pronounced, his eyes became injected, and he began to pull his hair. Excessive salivation and photophobia were noted.

Physical examination revealed a well developed child who appeared chronically ill. The pulse rate was 180, and the respirations were 30 per minute; the blood pressure was 135/110. The patient preferred to sit up and lean forward so that he could rub his feet with his hands. He was listless and irritable but co-operated for the examination. The hair was coarse and dry. Both conjunctivas were injected, and a small amount of purulent drainage was present. There was moderate mucopurulent nasal discharge. The mouth, teeth, gums and pharynx appeared normal. A miliary rash was present about the neck, axillas, trunk, groins and upper thighs. The palms and soles were red, moist and cold; many deep-seated vesicles and pustules were present over the palms and soles. Several fingers had paronychial infection. The neck was supple, the thorax normal, and the lungs clear to percussion and auscultation. The lymph nodes were not remarkable; the liver and spleen could not be felt. The musculature was normal, but there was evidence of recent weight loss. Neurologic examination was negative. Routine laboratory studies were noncontributory.

The mercury content of the urine was found to be 0.02 mg. per liter on one occasion, 0.05 mg. on a second, and 0.03 mg. on a third.* The source of mercury at first could not be ascertained since the parents denied any exposure. During the child's stay in the hospital, however, his condition was discussed with the grandparents. The grandmother then reminded the mother of an episode 4 weeks prior to the onset of the illness, when, on a visit to the grandmother's house, he had opened the medicine chest and had been found playing with a tube of ammoniated mercury ointment. He had smeared the ointment over his face and chest, and sufficient ointment was in his mouth to require its removal with a washcloth.

The patient was given a course of BAL for 10 days. During the first 48 hours after the initial injection of BAL, the symptoms were markedly aggravated. By the 3d day of treatment, however, he was improved, and on the 4th day he became interested in his surroundings and talked to the doctors and nurses. On the 10th, and last day of treatment all observers agreed that he was much improved. He continued to rub his palms and soles but was in much better contact with his environment and with the people around him. No significant change in pulse and blood pressure had taken place. The appetite was good; the miliaria had disappeared. Vesicles in the skin also disappeared, and sleep during the night was uninterrupted. The mercury content of the urine on the 9th day of treatment was 0.01 mg. per liter in the first sample, and 0.09 mg. in the second. On the day after treatment was concluded, the values were 0.08 and 0.23 mg. per liter in a first and second sample, respectively. The child returned home, and improvement continued. It was subsequently learned that a physician had given calomel to this patient and to his twin sister during the episode of illness 8 weeks prior to admission to the hospital and approximately 2 weeks after the ingestion of the ammoniated mercury ointment. No recognizable sequelae were present at the last examination.

*Normally, mercury is not present in the urine in measurable amounts. Mercury contents up to 0.01 mg. are not significant since they approach the limit of error of the method.[3]

Discussion

These cases of acrodynia following the ingestion of ammoniated mercury ointment are of interest because the history of mercury ointment ingestion was not obtained in 1 until ten years after the episode and was obtained in the other only through recollection of an accident by the grandmother when the parents had forgotten it. In Case 2 the disease appeared shortly after the exposure to mercury and was associated with abnormal amounts of mercury in the urine. The disease improved clinically and the amount of mercury in the urine increased after the administration of BAL. The relation of the calomel given by the physician to the pathogenesis of the disease is not clear. The twin sister also received calomel and acrodynia did not develop. It is a well known fact that few children who are exposed to mercury have the clinical manifestations of acrodynia. The patient may have been sensitized by the ammoniated mercury, so that the disease could have been precipitated by the calomel. We have not felt justified in exploring the mercury sensitivity of the twin sister by the deliberate oral administration of ammoniated mercury ointment.

Case 1 is of particular interest because of the late dental sequelae. Few long-term observations in acrodynia have been recorded, and the ultimate effect on developing dental structures has not been stressed. Loss of teeth and destruction of alveolar processes are well known adverse reactions to exposure to mercury.[2] Debré[4] and Cléret reported a recurrence of acrodynic symptoms seven years after an initial episode at three years of age. Their patient not only lost her deciduous teeth during the initial episode but actually sloughed portions of bone from the mandible. At the time of recurrence of symptoms her jaws were described as atrophic, resembling those of an aged edentulous person. The permanent teeth had failed to erupt, and presumably had been destroyed while in the dental-follicle stage. The atrophy of the alveolar ridge in Case 1, in the region where dental follicles were apparently destroyed by the oral lesions of acrodynia, is clearly demonstrated in Figures 3 and 4. That disfiguring adaptations of the jaws and remaining teeth did not develop is a tribute to the dental care this patient received. Careful dental evaluation of children with acrodynia is indicated so that proper orthodontic care may be provided before advanced complications occur.

Summary

Two cases of clinical acrodynia following the ingestion of ammoniated mercury ointment are reported. In 1, the history of ingestion was obtained ten years after the illness. In the other, the perti-

nent data in the history had been forgotten by the parents but were supplied by the grandparents after questioning had oriented the parents toward mercury as a possible causative factor. Destruction of developing dental follicles of the permanent teeth occurred in 1 patient and required extensive orthodontic treatment. Early attention to possible dental damage in acrodynia is stressed.

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THERAPEUTIC APPLICATION OF HEAT: ITS USES AND ABUSES*

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NO therapeutic procedure is more commonly employed in either a department of physical medicine and rehabilitation in a general hospital or the home than application of heat in some form. Numerous methods are available for the application of thermal stimuli to living human beings, heat, when it is employed therapeutically, being derived from several sources of energy — radiant, electric or sonic.

Radiant energy is the term applied to rays with wave lengths that in the electromagnetic spectrum are included between the "far" infrared energy band on the one hand (220,000 millimicrons) and the far ultraviolet portion of the spectrum on the other (200 millimicrons). Between these extremes lies the visible light spectrum, the source of luminous heat. The terms near and far used in connection with infrared and ultraviolet energy bands refer to their relation to the visible light spectrum. From the physical standpoint the difference between the rays that make up the several regions of the spectrum depend upon variations in intensity and wave length. Wave length is the distance between the crest of two adjoining waves of ether, analogous to the waves of the ocean. Wave lengths are measured in Angström units or millimicrons. Since these terms are frequently referred to in medical literature, their significance should be understood. An Angström unit equals one tenth of a millimicron or one ten millionth of a millimeter. Therefore, 1 millimicron is the equivalent of 10 Angström units.

Visible and infrared rays, the sources of radiant heat, differ from the rays derived from other parts of the spectrum in that their action is primarily thermal. Their application is promptly accompanied by a sensation of burning; erythema develops rapidly at the site of exposure. They have no biologic action; their effectiveness is due entirely to heat production.

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Radiant energy may be applied to the body by conduction or convection. When heat is applied by conduction, the energy is transferred by direct contact from the warmer to the cooler subject. This method is the easiest to carry out and has the greatest application. It includes such homely methods of heating as hot-water bottles, the direct application of other heated bodies, such as bricks, sand bags, irons, electric pads and blankets, hot compresses and hot packs. Conductive heating includes more elaborate procedures: fever cabinets, the use of hot moist air, devices in which hot water flows through various applicators and the useful paraffin bath. The energy from these conductive sources falls within the "far" infrared range of the spectrum. Hot baths and all hydrotherapeutic procedures that depend upon thermal stimuli for their effectiveness are methods of heating by conduction. These embrace whirlpool baths and therapeutic tanks and pools as well as contrast baths.

In heating by convection, the heat is transmitted through the air or atmosphere to the body from an outside radiating source. The heat thus derived falls within the infrared portion of the spectrum. It is said that the near infrared energy is therapeutically more effective than that which is emitted by the far infrared band. It is held that the depth of penetration of near infrared and visible rays is between 1.5 and 3.0 cm., whereas that of far infrared is probably not over 1 mm. There is some difference of opinion about the significance, from a therapeutic standpoint, of this variation in penetration. A relatively greater amount of near infrared radiation is obtained from luminous sources than from those that are nonluminous. For this reason, the latter sources of infrared radiation are not as popular as those that emit luminous and near infrared energy.

The commonest way of applying heat by convection is the use of luminous lamps, which utilize the radiant energy produced by carbon or tungsten filament bulbs, reinforced by suitable reflecting surfaces. An effective method of applying heat by

convection is the use of bakers. Bakers are luminous heaters composed of a varying number of light bulbs covered by a concave reflector. They are easy to handle and readily constructed, and can be made up in different sizes and shapes adaptable for use over various positions of the body. Their effectiveness is enhanced if the baker is covered with some insulating material, such as a blanket.

Nonluminous infrared lamps and generators consist of metal coils or plates, which glow a dull red when heated because of the resistance that they offer to the passage of an electric current. Here again reflectors are useful in concentrating the energy upon the part under treatment. The various types of commonly employed electric heaters are in effect nonluminous heating units that emit energy in the far infrared range. Since no type of infrared energy possesses much penetrating ability their therapeutic effect depends primarily upon the production of a sensation of surface warmth accompanied by the effects of counter-irritation and hyperemia.

The methods of heating discussed above are relatively slow. Unless their application is unduly prolonged, they bring about no significant, deep, effective heating. When it is desirable to produce heat in deeper tissues, the so-called "conversive" methods are preferable. This is accomplished by the conversion into heat of electromagnetic energy produced by high-frequency alternating currents. The heat is the result of the resistance of the tissue to the passage of the electric current, as well as, in all probability, the heat generated by the friction of electrons as they impinge upon each other during their rapid oscillations. Alternating currents used for the production of heat have a frequency so high that when they are applied to living muscle the ordinary neuromuscular response elicited by currents of low frequency does not occur. The most widely employed method of conductive heating is diathermy.

There are three types of diathermy available: long-wave or conventional diathermy, the oldest form; short-wave diathermy, now the most popular and almost universally used; and microwave diathermy, the most recent addition to this branch of thermal therapy. The therapeutic value of the application of high-frequency currents to man is due to the thermal reactions that they produce and not to any specific biologic effects. When high-frequency currents are locally applied in such a manner and with such power as to bring about tissue destruction the procedure is called "surgical diathermy." The application of such a current in such a way as to bring about only thermal and nondestructive effects is referred to as "medical diathermy."

In long-wave diathermy, a high-frequency current is generated by a succession of damped waves produced by a spark-gap type of oscillator. The wavelength used in the long-wave apparatus is about 300 meters and the current oscillates at the rate of 0.5 to 3.0 megacycles per second. Since, at present, long-wave diathermy is largely supplanted by more generally useful and easily applied short-wave diathermy, the former requires little more discussion.

In the hands of those accustomed to its use, long-wave diathermy has proved effective. It is held that it localizes heat better than the short wave and is more useful in the treatment of chronic pelvic inflammatory lesions.

The method most frequently employed by physicians and in departments of physical medicine for the production of deep heating is short-wave diathermy. With the short-wave apparatus the alternating current is generated by a vacuum-tube oscillator. The current attains a frequency of 10 megacycles per second at wave lengths of 30 meters and up to 100 megacycles per second with wave lengths of 3 meters. When short-wave diathermy is applied, the patient becomes either a part of a high-frequency condenser or a conduction field, depending upon the type of electrodes that are employed. When the condenser field is desired condenser pads, plates or cuff electrodes are used. For an induction field the electrode of choice is the induction cable applied around the part or as a "pancake" laid over the part. The drum electrode, a newer modification of the induction cable, is useful in certain conditions.

It has been held by some that short-wave diathermy produces selective tissue heating. Whatever differential heating occurs is due not so much to the wave length chosen as to the amount of power output and the technic employed. It is now generally agreed that the best results are obtained by the use of a cable electrode.

It is not surprising that short-wave diathermy has attained popularity among the medical profession and is so widely employed, since it gives more rapid and deeper penetration of heat than long-wave diathermy and is an easier, safer and more convenient method of applying deep heat. There are some physicians whose concept of physical therapy is limited to the use of diathermy. It should be emphasized that in whatever form diathermy is used or however it is applied, it has no specific biologic effects and its therapeutic results are entirely due to the production of heat.

More recently the third form of diathermy, known as microwave diathermy, has been developed. In this procedure, the physical properties of electromagnetic energy produced in a radar system are utilized to bring about deep localized heating. The microtherm generates energy in a continuous wave, air-cooled, magnetron oscillator tube connected to a director by a coaxial cable. This apparatus operates at a frequency of 2400 to 2500 megacycles per second, at a wave length of approximately 12.5 cm. and with a maximum power output of

125 watts. During the past few years, microwave therapy has been extensively employed and carefully investigated.

Microwave radiation brings about a more concentrated heating than short-wave diathermy, as well as a greater penetration of heat. The degree of heating and the depth of heating when this form of energy is applied depend upon the type of director used, the power output employed, the distance of the director from the skin and the duration of the treatment. Most observers state that microwave radiation causes a marked increase in blood flow. The greatest rises in temperature were noted in superficial muscles lying about 1.5 cm. beneath the skin. Elevations of temperatures of 2° to 5° C. were observed.

It should be noted that when microwave radiation is applied, patients experience a mild sensation of warmth. It is important to remember that the patient's sensory reactions alone must be used as an index of the amount of dosage. If the power output used is sufficiently great to cause a definite feeling of warmth on the skin, the deep temperatures, which are higher than the superficial ones, may well be elevated to a point that brings about tissue destruction. Microwave radiation shares the disadvantage of all methods of heating by high-frequency electrical currents in that there is no method by which the dosage delivered to the patient can be accurately estimated. Therefore, the subjective sensation of the patient, often unreliable, has to be depended upon to determine the dosage. All forms of diathermy find therapeutic usefulness in conditions that require the application of deep, penetrating heat.

The most recent addition to thermotherapy is the use of ultrasonic energy as a means of producing heat in tissues. Sound waves to be perceived by the ear as sound vibrate at a frequency of between 16,000 and 20,000 cycles per second. The ultrasonic waves used in therapy are identical with sound waves, except that their frequency is greater than 20,000 cycles per second. The machines at present used for ultrasonic therapy employ a frequency of about 1,000,000 cycles per second. Unlike electromagnetic vibrations, sound waves cannot pass through a vacuum; their propagation requires some material substance between the source of the sound and the area to be treated.

The ultrasonic apparatus produces ultrasonic energy by using a crystal of quartz or some other piezoelectric substance. In the "transducer" that houses the crystal, the energy derived from a high-frequency electric current is converted into mechanical vibration, which in turn produces sound waves. By means of what is known as a "sound head" these vibrations are transmitted through a coupling substance to the surface of the body, where they are converted into heat.

It has been shown that the heat generated by these rays can penetrate to a depth of 5 cm. or more. At present the therapeutic value of sound waves is, so far as is known, dependent upon the production of heat. It is recognized that ultrasonic energy may have other effects, probably mechanical and chemical. It is possible that some of the successful therapeutic results ascribed to ultrasonic therapy are due to these latter properties. Workers at the Mayo Clinic and elsewhere have demonstrated that ultrasonic therapy employed without due caution is capable of causing disastrous results, particularly destructive effects in the nervous system, spermatogenic tissues and at the epiphysis of growing bone.

This form of therapy has been used extensively in Europe, where many startling claims are made for its advantages. In this country thus far its use has been limited by an attitude of conservatism and caution that has developed. A final opinion of the clinical value of ultrasonic therapy depends upon further carefully controlled studies. It is reasonable to assume that ultrasonic therapy, judiciously employed by properly qualified persons, may prove to be a useful procedure both in therapy and in diagnosis.

Physiologic Effects of Heat

Changes induced by heat are complex and still poorly understood. Heat in any form when applied locally to an area of the body surface causes an increased rate of blood flow that is due to vasodilatation. This results in a rise in capillary pressure associated with an increased rate of transfer of fluid from the blood to the tissues, accelerated local metabolic activity and an increase in phagocytosis. The greatest rise of temperature occurs at the point of contact, where the energy exchange is greatest. After a sufficiently long period of contact with the heat locally, deeper structures, as the result of conduction, show a significant temperature rise. Excessive local temperature is prevented by the distribution of heat throughout the body by increased blood flow.

When a person is subjected to general heating of the body the most important effect is the production of fever. This results from a disturbance of the balance between the input of heat and its dissipation. A rise of body temperature of sufficient degree and duration is accompanied by sweating, increased respiratory and circulatory rates, alkalosis due to dehydration and hyperventilation and increased metabolism.

Indications for the Use of Heat

Thermotherapy can rarely be regarded as an isolated, definitive form of treatment. It is a useful and important adjunct when combined with other measures in the therapeutic regimen of many conditions.

It has long been known that the local application of heat is effective for the relief of pain, particularly that of neuromuscular origin and in arthritic conditions. The relief of pain in acute poliomyelitis by the use of hot packs is another example of this effect. How heat relieves pain is still not clearly understood. Hot packs, baths and various forms of radiant heat are widely used to bring about general relaxation and relieve muscular spasm. Therefore, heat is frequently applied before massage, manipulation or therapeutic exercises are undertaken. In the management of inflammatory conditions of muscles and fascia the use of radiant heat and hot compresses is almost routine.

In suitable cases of chronic arthritis appropriate forms of heat are most helpful. The methods most generally used are baking and other forms of infrared energy, as well as hot compresses, but of even greater help are whirlpool baths and paraffin packs locally and general hot baths for body heating. Diathermy and the microtherm have proved of less value than the above procedures in treating the arthritic patient. Electromagnetic energy increases the discomfort of and should not be used on acutely inflamed joints. Of late, ultrasonic therapy, by means of water coupling in a bath, has been tried in chronic cases of rheumatoid arthritis. The results obtained are unconvincing. In chronic degenerative arthritis, particularly of the hands or feet, encouraging results have been obtained with contrast baths.

The prolonged induction of high body temperature (above 104°F.), or fever therapy, is rarely employed today. The necessity for such treatment has been eliminated by the widespread use of the sulfonamides and antibiotics. Mild elevation of general body temperature (102°F. for not over two hours) has some value in generalized rheumatoid arthritis, in chronic infectious arthritis, when drug therapy is not effective, and in iritis, uveitis and interstitial keratitis of undetermined origin.

Contraindications

As is true of all effective forms of therapy, there are cautions to be considered in the use of heat. Extreme care must be exercised to avoid burning the patient. Even superficial and slight burns may cause considerable discomfort and seriously interfere with the progress of treatment. Burns may so disturb a patient's psychology that fear arises of all forms of physical therapy. Burns resulting from electric currents are especially troublesome because they cause considerable tissue loss, heal slowly and leave serious scarring.

The more intense forms of heating should be used with caution in very young children, in old people, in patients who are debilitated and in those suffering from chronic disease, such as diabetes, general arteriosclerosis, myocardial degeneration and chronic nephritis. Local heat should not be applied over areas of malignant degeneration. Nor should it be used in patients who suffer from hemorrhagic disease or over areas of hemorrhage.

Before heat is applied to older persons or those who have been injured, their sensory responses should be carefully worked out. If there is any sensory abnormality or impairment due to central or peripheral lesions of the nervous system, heat should be avoided or used with extreme caution.

Especial precaution should be remembered whenever short-wave diathermy is employed. The apparatus must be set up in such a manner as to prevent burning either from the electrodes or from the cable. There must be no clothing between the electrode and the skin — only the spacing material. Patients must remove all metallic objects from the region of the treatment. The chairs, tables and beds upon which patients are placed must be of wood and free of metal parts, including innerspring mattresses. Any sensation of pain or burning calls for immediate cessation of treatment. Patients should not be allowed to give themselves diathermy treatment. The material used for spacing and the area under treatment must be kept dry.

Diathermy is contraindicated in all acute processes associated with fever, suppuration or other local evidences of acute inflammation, including edema. Because diathermy increases regional blood flow, its application aggravates already present edema and congestions. Therefore, it increases the pain and disability when used during the early stages of trauma, sprains, fractures and in acute bursitis and arthritis. Diathermy is to be avoided during hemorrhage, even during profuse menstruation, and should not be applied over the lower back during pregnancy. It is contraindicated when cancer is present.

In the use of all forms of thermotherapy it is important to remember that there is real danger of bringing about disastrous results if even moderate degrees of heat are locally applied to the extremities of patients suffering from impaired peripheral circulation. When arterial flow is obstructed or impaired the use of even mild local heating causes an increased metabolic demand, which calls for more oxygen than can be delivered through the inadequate arterial flow. This creates a relative ischemia, with its attendant pain, edema, ulceration and even gangrene. Local heat is equally contraindicated in obstructive lesions of the peripheral venous circulation. As long as the arterial channels are open the demand for increased blood created by heating can be met. However, the inadequate venous return flow so interferes with the cooling and heat dissipation that the local tissue temperature rises to a point that causes edema, ulceration and pain.

Disregard of some of the physiologic changes that occur when heat is used has not infrequently been responsible for disappointing results from and unfavorable criticism of thermotherapy.

ACUTE APPENDICITIS DURING MENSTRUATION

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IT IS my impression, derived from over twenty years of experience in surgery, that acute appendicitis rarely occurs during menstruation. The records of three hospitals in the Boston area were studied in an attempt to verify this idea, and the cases of 725 women upon whom appendectomy only had been performed were reviewed. The pathologist reported acute appendicitis in 265 of these cases. In this group, operations were performed on 242 patients between the ages of eleven and fifty years, the age group taken as the possible limit of years during which menstruation might occur. The fact of the absence of a menstrual period at the time of operation was determined from the history or the recorded findings of physical examination. The records showed that appendectomy was performed in 10 cases during the first five days and in 14 on one of the terminal days of a period. Only 9 of these 24 patients operated on during the period gave evidence of acute appendicitis in some form. In other words, nearly two thirds of the patients admitted during a period, with a diagnosis of acute appendicitis and operated upon did not have acute appendicitis.

TABLE 1. *Day of Menstrual Period on Which Appendectomy Was Performed.*

AGE	DAY OF PERIOD	PATHOLOGICAL DIAGNOSIS OF APPENDICITIS
yr.		
Allerton Hospital:		
39	5	Acute
43	7	Acute
Booth Memorial Hospital:		
47	7	Acute gangrenous, with perforation
23	8	Recurrent acute
Mount Auburn Hospital:		
12	3	Acute
18	4	Subsiding acute
40	5	Acute
29	7	Acute
39	8	Subacute

Table 1 indicates the day of the period on which appendectomy was performed on the 9 patients in whom acute appendicitis was found. These figures suggest that acute appendicitis during menstruation is rare, since only 9 out of 242 women actually had acute appendicitis at that time. The remaining 15 patients operated on during the period gave no evidence of acute appendicitis. Six of these were operated on during the first five days, and 9 from the fifth to the eighth day of the period. Unfortunately, the records in these cases disclose no description of any other disease that may have been present. In some of these there was a history of "chronic appendicitis with pain occurring during periods." In others there was a history of vague "abdominal pain accompanied by nausea during a period." None of these 15 seemed to give a clear-cut indication of the reason for the operation. It may therefore be concluded that appendicitis was not the major cause of the symptoms.

The primary object of this paper is to draw attention to the facts presented in the previous paragraphs and to impress the general practitioner with the infrequency of this problem. With this knowledge on hand, it is less likely that patients will be rushed into the hospital for immediate operation. Secondly, it is obvious that a diagnosis of acute appendicitis calls for a proper appendectomy incision, and that such an incision makes it quite difficult to correct other disease present in the pelvic organs, which may actually be the reason for the train of symptoms. The third object is to consider conditions that, during menstruation, may simulate acute appendicitis and yet not require immediate operation.

It is not uncommon for patients with chronic retroversion to have abdominal pain with radiation into the right side of the abdomen; blood apparently backs up during a period through the redundant tubes, causing a certain amount of chemical irritation of the peritoneum. It is not unusual in such cases to find a slightly elevated temperature, tenderness and spasm of the abdominal muscles, accompanied occasionally by some rigidity. When a considerable amount of blood has accumulated, the patient may have nausea and vomiting as well. A similar chain of symptoms and signs can occur in endometriosis, because of the uterine-like activity of the endometrial implants. These also deposit blood during menstrual flow into the peritoneal cavity. On occasion, a bleeding chocolate cyst of the right ovary may produce the same picture.

Ordinarily, when blood has been deposited, the course of the patient's complaint is somewhat different from that found in acute appendicitis. Pain may develop in the lower abdomen, and usually does so prior to any other symptom. It is more vague in its location, although occasionally it is quite prominent, very low in the right side of the abdomen. This may impress the observer with the possibility of involvement of an appendix resting over the brim of the pelvis. Tenderness and spasm, however, are more elusive than in acute appen-

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dicitis. One may find a suggestion of spasm in the right lower quadrant of the abdomen and then a change in location of this sign, even during the course of the examination.

In my own experience, elective gynecologic surgery is rarely done during a menstrual period, although it has never been postponed if a period began after the patient was admitted to the hospital. It has seldom been performed for acute symptoms arising during the course of a period. In general, I follow the premise that during menstruation a train of symptoms and signs suggestive of acute appendicitis is nearly always due to some other condition. With this as a basis, it becomes evident that one must also carefully examine the pelvic organs in spite of the fact that most patients are reluctant to have this done during a period. This reluctance is also noticeable on the part of physicians and must be dispelled for greater accuracy in diagnosis.

With this thought in mind and with further observation the physician will usually be rewarded by subsidence of the acute picture. Many patients will therefore be treated medically during the menses and in time, after further study, will be relieved of the gynecologic problem causing the symptoms. Thus, two operations will become unnecessary — one for a "benign" appendix mistakenly removed during the period and one for the chronic gynecologic disease that is present.

The preceding statements are well illustrated by a case that had all the earmarks of acute appendicitis but turned out to be one primarily of pelvic disease. The case reported below demonstrates clearly the value of rectal or vaginal examinations during a period, and how one might also have been misled by the history, examination and laboratory findings. In addition, it demonstrates the use of the proper incision — in the low midline — when the patient was finally operated upon.

Case Report

R. S. (M. A. H. 90481), a 20-year-old girl, had started a regular period 2 days prior to admission to the hospital on May 22, 1951. About 6 hours previously, pain in the right lower portion of the abdomen, severe enough to cause her to leave work, had developed. This was followed, several hours later, by considerable nausea.

Physical examination disclosed tenderness in the right side of the abdomen and a suggestion of spasm. The leg-extension test was negative. The patient was able to sit up in bed without difficulty or increase of pain. On rectal examination, the uterus was found to be normal in size and position. The right adnexa were normal. The left ovary was about the size of an orange and rather tender.

The temperature was 100.8°F., and the white-cell count 19,500.

Several members of the resident staff and the family physician, who had not performed an examination of the pelvic organs, believed that the signs and symptoms were due entirely to acute appendicitis and urged operation. However, the patient was further observed. After the first 18 hours, the mild abdominal spasm disappeared, but she complained of a sensation of "fullness in the pelvis." The patient was operated on 3 days after admission, on the 5th menstrual day, because further rectal examinations disclosed the left ovary to be more tender and to have increased markedly in size.

After the abdominal cavity was entered through a low midline incision, the omentum was found to be stained throughout with brownish discoloration. There was free, blackish-brown blood in the pelvic cavity, partially filling the posterior cul-de-sac. The uterus was examined and found to be normal. Both tubes were examined and found to be normal. The right ovary was normal. The left ovary was enlarged to the size of a large orange, because of a large chocolate cyst, which had ruptured. As the ovary was displaced from the left vault, there was considerable spill of brownish-black blood from a hole in the capsule of the cyst. The ovary was further examined and a small portion of ovarian tissue, which appeared normal, was noted along the full length of the ligament. The entire cyst and some of the normal portion of the ovary were excised. The remaining ovary was reconstructed, a portion of the ovary that appeared quite normal in length and about 0.6 cm. wide being left. The old blood was wiped out of the pelvic cavity.

The appendix was next examined, and found to be quite long. The vessels were slightly injected. The serosa seemed thicker than normal. The appendix was removed. The abdomen was closed in layers.

The pathological report was as follows*:

The first specimen consists of an incomplete cystic structure, measuring (collapsed) 6 by 4.5 by 3 cm. Part of its wall is missing, and it is composed of one cyst. The surface is yellowish gray and glistening, with adherent reddish-brown material over approximately a third of its surface. The wall varies in thickness approximately 0.1 cm. to 0.6 cm. Part of the lining is grayish, smooth and glistening, but there is much reddish-brown material adherent to the surfaces of the lining. Multiple sections through the cyst wall show several cystic spaces, some of which contain coagulated blood. The cyst linings are smooth.

The second specimen consists of an appendix, measuring 6 cm. in length and having an average diameter of 0.6 cm. The surface is graying, tan, smooth and glistening. There is a moderate amount of fat attached along one border. The lumen is patent throughout. The wall is thickened, especially in the distal third. The lumen contains a little light-brown, semiliquid material. The mucosa is intact, but is flattened, where the lumen is slightly dilated, at about the junction of the distal third and proximal two thirds.

There is endometriosis of the ovary, which shows a large endometrial cyst with resorptive reaction to recurrent bleeding (chocolate cyst) and multiple cystic graafian follicles. In a few areas the endometrial cyst lining is preserved, with signs of proliferation. There are some adhesions and reaction to fresh hemorrhage on the surface of the ovary. There is no evidence of cancer. In the three sections of appendix the lumen is patent, and the wall is everywhere intact. The lumen contains small collections of poorly preserved polymorphonuclear leukocytes. The mucosa is well formed, but moderately rich in eosinophils. The submucosa is fibrous; the muscularis is moderately edematous and shows a light eosinophilia. The serosa is thickened and richly infiltrated with histiocytes.

The diagnoses are: old healed appendicitis with scarring of the wall and signs of a more recent healing appendicitis with pus in the lumen and edema and eosinophilia of the wall. The serosa is the seat of a low-grade chronic resorptive inflammatory reaction consistent with regional endometriosis. At this time, the appendix is not involved in the early stages of an acute inflammatory reaction, but shows a subsiding or healing phase of inflammation.

The patient was discharged from the hospital on May 31, 1951, and was last examined on April 8, 1952, when she was well, with periods that were regular and not painful.

Discussion

It is worth considering the difficulties that would have been encountered if this patient had been operated on for "acute appendicitis" when first seen. First of all, she would not have been cured. Secondly, two incisions during the same operation,

*Examination performed by Dr. Harold E. MacMahon.

or two separate operations, would have been necessary to effect a cure, since the enlarged left ovary was firmly adherent to the posterior aspect of the left broad ligament.

The only reference* that I have been able to find described 3 cases of acute appendicitis during menstruation occurring in a series of 800 patients upon whom appendectomy was performed at the Binghamton City Hospital. To this is now added 9 more out of 242 operations for acute appendicitis during menstrual age.

In the case presented above, involvement of the appendix with endometriosis is of interest, because of the early age of the patient.

Summary and Conclusions

The records of 725 cases of acute appendicitis occurring in women are reviewed. These patients were operated upon at three different hospitals by various surgeons. Nine cases only occurred during a period.

A case in a twenty-year-old girl with symptoms suggesting acute appendicitis at the start of her acute illness is reported. These subsided in about eighteen hours. Three days after her illness began, a ruptured left ovarian cyst, enlarged because of endometriosis, was removed at operation. The appendix was also involved with endometriosis.

Both organs were treated surgically through a midline incision. The ovary could not have been reached through a routine appendectomy incision, and another incision would have been necessary if the patient had been operated on when first seen.

The answer to the question whether acute appendicitis occurs during menstruation seems to be that it rarely does.

The only reference available in the literature disclosed 3 cases of acute appendicitis out of 800 appendectomies on female patients. In the study presented above the records of 242 women during possible menstrual age were surveyed. Nine cases only showed some form of acute appendicitis during a period. The rarity of acute appendicitis during menstruation is thus clearly demonstrated.

Fifteen other patients in the series studied were operated on during menstruation. Acute appendicitis was not found in these cases. Furthermore, the records do not give a clear picture of the indications for operation. Therefore, it seems that a longer waiting period and complete examination might have obviated these procedures.

It is suggested that vaginal or rectal examination during menstruation be performed and that modesty on the part of the patient and reluctance on the part of the physician for such an examination be overcome.

Furthermore, it is believed that nearly all patients with acute symptoms in the lower abdomen and pelvic cavity occurring during a menstrual period can safely be observed. Such a study, it is believed, will do away with needless operations and will allow better surgical care of the patient when the time for it has arrived.

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MEDICAL PROGRESS

DIABETES MELLITUS

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IN THIS report the following aspects of diabetes mellitus are considered: biochemistry and physiology; pathology and pathogenesis; experimental diabetes; diagnosis; treatment; associated conditions; surgery in diabetes; pregnancy in diabetes; and complications.

BIOCHEMISTRY AND PHYSIOLOGY

Carbohydrate Metabolism

The recent use of C^{14}-glucose has advanced understanding of carbohydrate metabolism. For example, it has yielded more accurate estimates of the disposal of fed carbohydrate in the normal organism: 80 per cent is oxidized,[1, 2] and 17 per cent[3] and 3 per cent converted to fatty acids and glycogen, respectively. In vivo studies of diabetic animals showed a double turnover rate of glucose that was due mainly to an increased intake and glycosuria. However, the glucose oxidation rate was still surprisingly high (66 per cent of normal), and even the liverless animal could still oxidize 25 per cent of injected glucose.[4, 5] The main defect was in lipogenesis: rat-liver slices showed a sixfold decrease in this function as compared with a threefold decrease in glucose oxidation.[5]

Attempts to clarify the defect in diabetic metabolism have centered about Cori's original work. He concluded that the block was at the hexokinase reaction, which converts glucose to glucose-6-PO_4, and that insulin had no independent function, serving merely to neutralize the continuous, inhibiting activity of pituitary and adrenal hormones. Because of repeated failure to reproduce his results in tissue homogenates, interest shifted to intact liver slices or muscle, and to in vivo experiments.

Using C^{14}-glucose, -fructose and -acetate, Chaikoff[6] was able to demonstrate two separate blocks in the utilization of these substances by the diabetic as compared with normal liver slices. He measured the rate of oxidation of all three and found that of the three glucose alone could not be oxidized. This located the primary block at the hexokinase reaction and at the same time implied the normalcy of the rest of the oxidative enzyme system.† Secondly, he found lipogenesis impaired for all three: the inclusion of so simple a glucose metabolite as acetate in these experiments indicated that this block must be in the pathway of conversion of "2 carbon-like" metabolic derivatives of glucose to fatty acids. Thus, the first of Cori's concepts has received confirmation.

Others have tried to prove that the only action of insulin is physically to facilitate the passage of the glucose molecule across the cell membrane and thus into the metabolic pool.[9] Drury and Wick,[10] however, showed that cells are really impermeable to glucose as such and that the penetration facilitated by insulin was by a chemical reaction. The sharp specificity of its action is illustrated by the fact that it does not act on sorbitol, which differs only slightly (in the terminal carbon atom) from glucose, so that it probably involves an enzyme transformation.[10, 11]

Meanwhile, it has been conclusively shown that insulin promotes carbohydrate metabolism by a positive and independent action, not requiring the presence of the pituitary and adrenal glands.[12-14] Thus, Cori's second concept is not confirmed.

In vitro attempts to restore diabetic metabolism to normal by the addition of insulin have not been completely successful. Both glycogen synthesis[12] and glucose oxidation[12] in the diaphragm of the diabetic rat have fallen short of the mark — by 50 per cent in the latter. Lipogenesis, the metabolic pathway that is blocked most in diabetes, is restored least by addition of insulin to liver slices from the diabetic rat. In the latter preparation, if the diabetic animal had been pretreated with insulin for a minimum of three days before being killed, the defect in lipogenesis was repaired completely (tenfold), and oxidation somewhat less completely (twofold).[15] Such experiments suggested that deterioration of some vital metabolic process had occurred during the period of insulin lack.

The nature of the mechanism is suggested by previous studies on the conversion of C^{14}-labeled acetate to fatty acids in normal liver slices. Although that process was not enhanced by the addition of insulin alone, it was increased by insulin and pyruvate, which is a product of normal carbohydrate metabolism.[16] Chaikoff has recently obtained similar results in the lipogenesis of diabetic liver slices. If the diabetic animals, instead of being pretreated with insulin, were prefed with fructose, there was a pronounced increase in the synthesis of fatty acids from lactate and acetate, but not from glucose. Apparently, fructose could be metabolized in the

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†This has been confirmed very simply in vivo in both animals and man by the demonstration of the continued ability of the diabetic subject to utilize glucose-1-phosphate and fructose, which enter the metabolic cycle without the hexokinase reaction.[7, 8]

diabetic organism and thereby supplied the products of intermediate carbohydrate metabolism needed to facilitate normal lipogenesis from all three substances; glucose itself, however, still could not be converted to fatty acid because its primary hexokinase block still remained unaltered.*[17]

Brady and Gurin[18] studied the synthesis in liver slices of long-chain fatty acids and cholesterol from acetate (2 carbon) and octoanate (8 carbon) and found that insulin could enhance the process by 50 to 125 per cent. In (alloxan) diabetic liver slices the synthesis of the fatty acids from each of these was reduced to one fifth to one twentieth of normal; this process could not be restored to normal by insulin (alone or with glucose-6-PO_4). The authors drew the conclusion that "the transfer of energy required for fat synthesis is derived mainly from a coupled reaction involving the simultaneous oxidation of some normal carbohydrate intermediate." The same diabetic liver slices could still synthesize cholesterol. Thus, in diabetes with the reduction of normal fat synthesis from 2-carbon fragments, such fragments are then more freely diverted to the pathways of ketone and cholesterol formation.[18]

A previous review cited the evidence for other sites of action of insulin close to the tricarboxylic acid cycle.[19] It has therefore seemed reasonable to search for a single more fundamental biochemical action to explain such apparent versatility of insulin, perhaps "in the interplay between enzymes forming and degrading high energy phosphate so as to favor the increase in high energy phosphate."[20] One such enzyme, coenzyme A, has been suggested as an acetyl carrier in the process of fat and protein synthesis. With this in mind, Charalampous and Hegsted[21] investigated the rate of acetylation of para-aminobenzoic acid in the normal versus the alloxan-diabetic rat and found it to be definitely decreased in the latter. It took twenty-six days of diabetes for the defect to appear and ten days of insulin therapy to correct it. This is of interest with respect to the pretreatment time required to condition alloxan-diabetic livers for insulin action. In addition, it was found that an increase in dietary fat performed the same service even more quickly than insulin. This last observation is explained on the assumption "that the energy derived from the breakdown of fat may be made available as ATP without the intervention of insulin." This has had its counterpart in the therapy of experimental diabetes when really high fat diets (70 per cent fat) could reduce glycosuria, reduce ketosis and result in more glycogen deposition than 40 per cent fat diets.†[22] This work suggests that glycogen is formed from intermediate products of fat metabolism and that there is a process of enzyme adaptation for fat utilization in the absence of insulin as a mechanism for metabolic adjustment.

*This suggests a parallel with the need for a high-carbohydrate diet prior to a glucose tolerance test.

†This is reminiscent of old clinical experience in the efficiency of isocaloric high-fat diets in the therapy of diabetes.

Growth Hormone and Protein Metabolism

For a more complete understanding of carbohydrate metabolism and the role of insulin, the action of the pituitary growth hormone must be discussed in greater detail. The dual role of this hormone has been more clearly defined by recent work. The best known action is the inhibition of carbohydrate metabolism, which is strictly peripheral‡[24] and which also occurs in the depancreatized animal.[14] Insulin sensitivity can be used as a measure of this action. This was shown to be increased sixty times after hypophysectomy and could be restored to normal by a dose of growth hormone that was small compared to that needed to produce pituitary diabetes.§[26]

The second effect, a hypoglycemic action, has only recently been discovered.[27] This occurs immediately after injection of pure growth hormone and lasts only eight hours. It probably represents a stimulation of insulin production, for it requires the presence of the pancreas. For this action, too, the dose required is far below the diabetogenic dose.

To understand the possible biologic function of these apparently opposite actions of growth hormone, one must turn to protein metabolism. In the normal organism, the processes of protein synthesis and breakdown are in constant dynamic equilibrium with the amino acid pool. This includes a large portion of — even though not the entire — muscle mass of the body.[28] Although a number of hormones participate in the maintenance of this equilibrium,[29] growth hormone and insulin are the most important. Of the two, the first is dominant. However, a minimal amount of insulin is required to avoid the striking catabolic effects of diabetes. In uncontrolled diabetes, protein synthesis is reduced threefold to fivefold as measured by the rate of incorporation of S^{35}-methionine into muscle protein.[30] At the same time, the increase in plasma and urinary amino acids has been used as a measure of the increased protein breakdown. The proportions of the amino acids found indicated not merely simple protein catabolism but also excess new formation of specific amino acids such as alanine and glycine.[31]

After enough insulin is supplied to prevent protein catabolism, extra insulin is needed to maintain normal protein synthesis. The amount is quite substantial, three to five times that needed to prevent gluconeogenesis.[14] In fact, a mathematical relation between the amount of extra insulin administered and the protein synthesized may be demonstrated.[32] Yet both hormones are necessary since neither one

‡In the process of lipogenesis from acetate, a stimulating effect of insulin and an inhibitory one of the pituitary gland have also been shown, both exerted peripherally.[25]

§A similar inhibiting effect of the adrenal gland has been localized to the zona fasciculata, which is the source of the carbohydrate-active steroids.[26]

alone can maintain the normal rate of protein synthesis in the Houssay (hypophysectomized-depancreatized) animal.[14] From this point of view, one can understand the usefulness of the two actions of growth hormone: to stimulate both the production of extra insulin and the inhibition of carbohydrate utilization to provide materials for the protein synthesized.

Since the two actions of growth hormone increase the work of the pancreas, Young has suggested that an increased rate of secretion of the pituitary over a long enough period could eventually exhaust the pancreas and cause diabetes in human beings. The dosage needed for these actions is small, so that it is conceivable for these effects to occur without producing acromegaly. However, it is also true that the dosage is well below that known to cause diabetes in animals in a reasonably short period.

Miscellaneous Considerations

Soskin has maintained that elevation of the blood sugar concentration increases the utilization of glucose. The rate of oxidation or lipogenesis has recently been shown to be equal in the presence of a normal as compared to an elevated blood sugar level (500 to 1000 mg. per 100 cc.).[3, 33] This deprives hyperglycemia of any claim to a physiologically useful role in diabetes.

The glucose equivalent of protein has been reinvestigated in depancreatized dogs because old methods had erroneously assumed lack of glucose utilization by the diabetic organism. Drury has now derived a new value of 90 to 95 per cent (versus 58 per cent) potential glucose in the amino acids of protein. This finding is of less practical importance now than in the preinsulin era because long-acting insulin can adequately handle the slowly released glucose derived from protein.[34]

The normal renal-threshold value by chance coincides with the maximum blood sugar level desired (180 mg. per 100 cc.); this fact has rendered urinalysis a useful as well as a convenient index of hyperglycemia. Any information that indicates how it may vary dynamically has practical value. Recently, it has been shown that insulin therapy of diabetes may lower the threshold significantly.[35] Therefore, sole reliance on urine tests without determinations of blood sugar during the course of treatment might lead to erroneous conclusions. Similarly, the administration of ACTH had been said to lower the renal threshold. This has recently been proved erroneous,[36] so that all glycosuria occurring during ACTH therapy should be considered a result of its metabolic effects.

The mechanism by which work increases carbohydrate utilization in the diabetic patient has been a source of speculation. In experiments on severely diabetic rats, Ingle et al.[37] administered ample insulin at the same time that they measured the work output of the leg muscles. The supply of carbohydrate was limited, and in the competition with the insulin for this substrate, the work output fell to less than 50 per cent of normal. This indicates that the pathways of utilization of carbohydrates are probably different for these two processes.[37]

Pathology and Pathogenesis

The Pancreas in Diabetes

The inability to recognize pathologic abnormalities in the pancreases of all diabetic persons has been a puzzling discrepancy. Warren[38] had a residue of 26 per cent normal pancreases, Bell[39] 22 per cent and Terbrüggen[40] 20 per cent. Terbrüggen had added the calculation of the alpha-beta cell ratios as a simple and better semiquantitative method of estimating an insufficiency of secreting beta cells. This ratio was diagnostically low only in the younger diabetic persons (under the age of forty).

In a recent study of the pancreases of 46 diabetic and 40 normal subjects, Hartroft[41] used two additional diagnostic features: beta granule size and reduplication of the basement membrane of the islet capillaries. Combining these criteria with the usual indexes,* he could reduce the incidence of normal pancreases found among diabetic persons to a new low figure of 11 per cent.

However, the fact that certain pathologic features prove useful in the diagnosis of diabetes does not necessarily indicate their pathogenetic significance. For example, Bell[39] and Terbrüggen[40] both believed that hyalinization alone was not of primary significance; in fact, it is conceivable that both hyalinization and the reduplicated basement membrane are secondary effects of the diabetes. Hydropic degeneration has been proved experimentally to be a secondary phenomenon. Recent studies have revealed that the hydropic vacuoles of the pancreas consist of glycogen, as in the kidney,[42] in which this phenomenon is closely dependent upon the degree of the hyperglycemia (350 mg. per 100 cc.) and is reversible.[43] In the pancreas, its appearance can be prevented by small doses of insulin even though some hyperglycemia persists.[44] Accordingly, the widespread use of insulin may perhaps explain the relative rarity of this finding in human as compared to experimental diabetes. It is also evidence in favor of the initial use of insulin in diabetes of borderline severity.

Hartroft[41] found that only 6 out of the 46 pancreases among diabetic persons (13 per cent) showed advanced diabetic changes; the remainder demonstrated all intermediate degrees of decrease in islet tissue, beta cells and granules. Wrenshall and his associates[45] expanded this group to 213 pancreases (65 of which were diabetic) and at the same time

*These are strikingly decreased islet-tissue mass, hyalinization and higher degrees of hydropic degeneration of beta cells.

determined their extractable insulin content. His findings are very important. The cases fell into two main categories as far as age, pathology and insulin content were concerned. The younger group of patients whose diabetes had begun before the age of twenty-three* had a striking loss of islet tissue and an average extractable insulin content per gram of pancreas of less than 3 per cent of the values for nondiabetic controls.† By contrast, in the remaining patients whose diabetes started after the age of twenty-three ("maturity-onset" group), the pancreases showed the intermediate type of pathological findings and an insulin content 47 to 60 per cent of normal.

No explanation could be found for the sharp differentiation of the groups by age. Age variations have been noted in the response of the insular tissue of the pancreas to a variety of experimental conditions in animals. Any attempt to link it up with an excess of growth hormone activity of the pituitary gland is at present purely hypothetical; besides, 1 of the cases of acromegaly and diabetes showed an insulin content of 50 per cent of normal. Of greater moment is the fact that the pancreases of most animals with experimental diabetes have an insulin concentration less than 10 per cent of normal, whereas the average human diabetic pancreas has four to six times that level. At least two explanations have been offered for this discrepancy in human subjects: that there is a combination of decreased insulin formation and a block in release of the insulin from the pancreas; and that one must postulate an extrapancreatic block in the activity of insulin. The determination of blood insulin levels would be valuable information toward solving this problem.

Insulin Content of Blood

By coincidence, two investigators have recently succeeded in measuring the blood insulin of man for the first time. Bornstein[46] utilized the blood sugar depression in an insulin-sensitive test rat and Willebrands et al.‡[47] used the young rat hemidiaphragm in vitro. Both methods gave consistent and similar results. Bornstein found the normal fasting blood insulin to be 0.1 milliunit per cubic centimeter. Since this was too close to the sensitivity of the method, he had to use the blood insulin two hours after oral administration of glucose; this is normally about 0.34 milliunits per cubic centimeter.§ This higher value could then be used for comparison with diabetic patients, in whom zero values indicated amounts lower than the method could detect, rather than absence of insulin.[48]

The blood insulin results fell into three distinct groups: no detectable blood insulin was found in many untreated diabetic patients, in all coma cases, in 2 untreated acromegalic patients and in 2 treated insulin-resistant cases¶[49-51]; the remainder of the untreated diabetic patients had widely varying amounts of insulin in their blood, with an average of 70 per cent of normal; and after treatment the values in all except the insulin-resistant cases were practically normal, even those with no detectable insulin before therapy.[51]

Among the untreated diabetic patients, it could be stated roughly that those with no detectable blood insulin were usually the ones with metabolic decompensation as shown by much weight loss and ketonuria. Many, but not all, were young. It is dubious whether it is justifiable to make a fundamental classification of diabetes on the basis of whether or not insulin is detectable in the blood.[52] There may very well be a parallel between low blood insulin and severe islet atrophy of the pancreas.|| However, this has not yet been investigated. The dynamic quality of the pancreas is emphasized by the reappearance of blood insulin after therapy.**

These facts indicate that the relatively high pancreatic insulin of most diabetic persons (47 to 60 per cent of normal) is accompanied by a correspondingly high blood content of biologically active insulin. Bornstein could detect no direct inhibitor of insulin in the serum of any of the three groups. He did discover that the serum of the patients with no detectable insulin had a delayed (four or more days after injection) inhibitory effect upon the test rats, rendering them refractive to the effect of insulin for three or four weeks.[50] This inhibition acts peripherally in the rat,[54] and it resembles in its action and chemical properties a brain hexokinase inhibitor previously found in untreated diabetic patients.[55] However, both inhibitors disappear after the treatment of the diabetes, and this phenomenon is probably secondary to the insulin lack.

Pathogenesis in Man

The facts to date imply that the only human diabetes that has been clearly proved to be entirely pancreatic is that of young patients with little remaining islet tissue or pancreatic or blood insulin. The vast majority of diabetic persons show too small a decrease in these indexes to account for the metabolic deficiency if their disease is compared quantitatively with experimental pancreatic diabetes. Either the human being is extremely sensitive to milder degrees of insulin deficiency or some

*"Growth-onset" group, so named because this corresponds to the period before active growth ceases.

†To this group could be added 9 patients of all ages who had died in coma; they differed only in that in many the ages exceeded twenty-three years. The one exception was a patient with insulin resistance who died in coma, the pancreas containing 33 per cent of the normal amount of insulin.

‡By this method they measured mainly the conversion of glucose to glycogen (70 per cent) under the influence of insulin.

§The contour of the blood insulin curve found in the glucose tolerance test confirms the Staub phenomenon discovered by previous indirect, cruder methods.

¶The serum of the acromegalic persons actually raised the blood sugar of the test rats and each of the patients with insulin-resistant cases had just received 300 units of insulin.

||It should be recalled that Wrenshall found the least amount of insulin in the pancreases of those who were young, had severe islet deficiency or died in coma.

**The exogenous insulin of therapy contributes a little to the blood insulin but not enough to account for the change.[53]

unknown inhibitor of insulin action must be postulated. None has been found, and the evidence to date is against an excess of either growth hormone[56] or ACTH* as the offending agent.

Whatever the pathogenesis of human diabetes, the element of heredity still remains as the basis for its development. However, confusion still exists regarding the exact pattern of inheritance. Watson and Thompson[60] have shown that the presence of the disease in the parents doubles the chances of its occurrence in the offspring. Recently, interesting data regarding age at onset have appeared. In the first place it was shown that the earlier the age at onset, the higher the percentage incidence of a positive family history.†[62] Moreover, diabetes was shown to develop at an earlier age in those whose parents were related however remotely and in the siblings of those in whom it occurred early, but there was no correlation with age at onset of diabetes in parents.[63, 64] Thus, age at onset of diabetes crops up again as a differentiating characteristic in the inheritance of the disease.

These facts have shed some additional light on the mode of inheritance. However, the basis for the inherited predisposition is not yet recognizable by pathological examination of the pancreas and must be presumed to reside in some inherited biochemical defect.

Experimental Diabetes

There is now experimental evidence not only of diabetogenic but also of pancreatropic factors, which Mount[65] has demonstrated in crude fresh saline pituitary extracts. Houssay[66] and his group found such activity in the general group of estrogenic substances, endogenous or synthetic. These protect 95 per cent of pancreatectomized rats from developing frank diabetes; their action is a local or systemic stimulation of hypertrophy and hyperplasia of the islands of Langerhans. Male sex hormones have the reverse effect.

Diagnosis of Diabetes

In an effort to discover the million patients with unrecognized diabetes, many public surveys have recently been made and have yielded much valuable information. Urinalysis is the simplest test for such surveys. However, it was found that when patients were relied upon to test their own specimens, only 50 per cent responded, and only 1 out of 6 with positive tests sought medical care. An ingenious new technic may be the answer.[67] It consists of a special absorbent material attached to a card, which can be dropped into the mail for testing. This has been applied at the state level and may be sponsored by the American Diabetes Association on a national scale.

The public survey conducted in Brookline, Massachusetts, used both urinalysis and a blood sugar test taken after an adequate meal (25 gm. of carbohydrate). Glucose tolerance tests were then performed on persons with abnormal urine or blood tests.‡[68] This survey discovered 2.2 per cent cases of diabetes among 3186 adults. The relative sensitivity of the urine as compared with the postprandial blood test may be inferred from the fact that the former by itself would have detected fully 56 per cent of all the cases, and the blood sugar alone 82 per cent. The latter was not 100 per cent sufficient by itself but was 50 per cent more sensitive than the urinalysis, especially for the patients with milder diabetes. So far as the selectivity of the two methods is concerned, diabetes was discovered in only 36 per cent of those with glycosuria but in 49 per cent of those with abnormal blood sugar.

If the glucose tolerance test could be made to approach the postprandial blood sugar in simplicity, the general problem of diagnosis would be made much easier. The fasting blood sugar of the glucose tolerance test is usually normal in the milder cases and may safely be omitted. The indexes of the one-hour peak value or the duration of return to normal may not both be abnormal in the borderline case. The interpretation of such atypical cases has long been a most difficult problem. Some have made the unproved assumption that only the duration is significant and have advocated the adoption of an oral glucose tolerance test using only the two-hour blood sugar level.§[69, 70]

Others have tried to improve diagnosis in borderline cases by the use of the blood phosphorus.[71] This decreases as a function of the entrance of hexoses into tissues[72] and is dependent on the presence of an insulin-secreting pancreas.[73, 74] However, recent results have shown that there is too much overlap between normal persons and those with mild diabetes for this test to be relied on for differential diagnosis.[75]

For a definitive decision whether the abnormal peak blood sugar value has diagnostic significance the most critical test to apply is the subsequent course of the patient. Rabinowitch[76] utilized for this purpose a ten-year follow-up study of a large group of patients whose sole abnormality was a single episode of asymptomatic glycosuria. After a decade, diabetes developed in 29 per cent of these, even if the glucose tolerance test had originally been normal. However, if the one-hour peak alone had been abnormally elevated even with a curve of normal duration, the incidence rose to 40 per cent. This peak value might also be useful in detecting a delay in emptying time of the stomach

*Neither an elevation of blood ACTH[57] nor a significant reduction in blood glutathione has been found in uncomplicated human diabetes.[58, 59]

†However, the phenomenon of anticipation — that is, the occurrence of the disease at a progressively earlier age in succeeding generations — does not occur in diabetes.[61]

‡Urine with over a trace of sugar (0.7 per cent or green with precipitate by Benedict's solution) or blood sugar of 180 mg. per 100 cc. or above half an hour to one and one-half hours after the meal.

§The maximum normals at two hours were considered to be a blood sugar of 120 mg. per 100 cc. after 50 gm. and 140 mg. per 100 cc. after 100 gm. of glucose.

with a resultant lag type of curve.[77] These facts seem to warrant the continued use of both the peak blood sugar value and the duration of the curve in the glucose tolerance test. Of equal significance, they lead to the recommendation that any patient with glycosuria, even with a normal glucose tolerance test, should be considered potentially diabetic and so treated.*

I have introduced a simplified, so called "modified" oral glucose tolerance test at the Beth Israel Hospital, where it has proved satisfactory in routine use for the past five years. This procedure employs 100 gm. of glucose and measures only the one-hour and two-and-one-half-hour blood sugar† and urine values. With only two blood tests, it still gives all the critical information required.

(To be concluded)

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MEDICAL INTELLIGENCE

TWO UNUSUAL CASES OF ECTOPIC GESTATION*

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DURING the past twenty years of a general surgical practice in two small community hospitals (under 50 beds) 25 patients with extra-uterine pregnancy have been operated upon.

Twenty-three of these cases were the more common type of rupture with tubal pregnancy. One case was a repeat — a rupture in a tubal pregnancy on the left one year after rupture of the right tube.

The remaining cases were much rarer: a full-term abdominal pregnancy, with living mother and baby; and an ovarian pregnancy, with co-existing intra-uterine pregnancy.

A review of the literature discloses many references to abdominal pregnancy. Renner[1] notes that Charles McKnight, about 1790, was the first American to perform a laparotomy for abdominal pregnancy. John Bard removed a nine-month-old fetus from the abdominal cavity fifty years before McDowell performed his now famous ovariotomy.

Beck[2] reviewed the literature from 1809 to 1919 and found 262 cases of abdominal pregnancy with living fetuses past five months. Lull[3] noted 321 cases of abdominal pregnancy with viable fetuses in the literature from 1813 to 1938.

Broomes[4] found only 21 cases of abdominal pregnancy in the world literature between 1935 and 1949. At this time there were about 2,500,000 babies born annually in the United States alone.

Hellman and Simon[5] reviewed the literature up to 1935 and added 5 cases, bringing the total of reported cases to 316. Dorman,[6] in the latest report reviewed, brings the total number of cases of abdominal pregnancy, with his own, to 566.

There is considerable discussion in the literature regarding just how the abdominal pregnancy has its beginning. The true primary peritoneal pregnancy is doubtful. Studdiford[7] gives the following criteria for primary peritoneal pregnancy: both tubes and ovaries must be normal, with no recent or remote evidence of injury; and there must be no evidence of uteroperitoneal fistula. Studdiford[7] states that some authors are doubtful about the occurrence of primary peritoneal pregnancy, and cites Novak as concluding that such an anomaly is impossible.

Presumably, the origin of primary peritoneal pregnancy is the meeting and implantation of the spermatozoön in the ovum at some point between the ovary and the fimbriated end of the fallopian tube in free peritoneal space. However, the expulsion of the impregnated ovum from the fimbriated end of the fallopian tube would cause no injury to the tube.

Broomes[4] describes three methods of treating the placenta in cases of abdominal pregnancy:

Group I — 3 cases in which the placenta was removed, with no maternal deaths but with only 1 living fetus. There was 1 secondary operation. The average stay in the hospital was three weeks.

Group II — 6 cases in which marsupialization, packing and drainage were employed. Four cases required secondary operations for complications.

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There were 3 maternal deaths. The average stay in the hospital was four weeks.

Group III — Twelve cases in which the placenta was left *in situ*. Six patients had stormy convalescences, reoperation was necessary in 3 cases, and there were 3 maternal deaths. The average stay in the hospital was four weeks.

Reed[8] left a placenta *in situ* in a case of abdominal pregnancy. Four years later at cesarean section, the residual placenta was found as a pedunculated mass on the posterior surface of the uterus; it was excised.

The fullest account of mortality statistics comes from Hellman and Simon.[5] In their 316 collected cases, 158 babies lived eight days or longer. The mortality report of 212 mothers showed 101 deaths. Mundell[9] states that for every 41 living extrauterine babies 8 will be deformed.

The symptoms are few, other than those of a normal nine months' gestation period. If the fertilized ovum is expelled from the fallopian tube, there may be vaginal bleeding between the first and third months of gestation. Fetal movements are apt to be noticeably painful.

The diagnosis of abdominal pregnancy is not often made unless the condition has progressed long past the nine months' period and the fetus has become calcified. I saw the late Dr. J. C. Hirst, of Philadelphia, remove a calcified fetus from the abdomen fourteen months after conception.

Case Reports

Mrs. F. W., a 27-year-old multipara in her second pregnancy, was admitted to the Webster District Hospital, Webster, Massachusetts, on July 2, 1951. Her first child had been born normally. The 1st day of her last menstrual period had begun on September 24, 1950. There had been no vaginal bleeding at any time during the pregnancy.

A few weeks before term her physician had noticed that the fetus was in a transverse position. The patient's only complaint was that fetal movements were really painful. Vaginal examination revealed that the cervix was not at all dilated. A mass palpated in the cul-de-sac was thought to be a pedunculated fibroid or an ovarian cyst. No pelvic tumor had been found before this pregnancy. At term, the patient was admitted to the hospital for x-ray studies. X-ray examination revealed a single fetus upturned in transverse position, with the head to the maternal right in lateral flexion; the fetal extremities were to the maternal left. The most dependent portion was a hand. There was a homogeneous haze filling the anterior and positive portions of the pelvis, but no definite soft-tissue mass was outlined. Considerable feces present in the rectum obliterated the view of the pelvis. It was the opinion of the radiologist that there was a single fetus in transverse position with the fetal head in lateral flexion on the maternal right and with the hand presenting. There was a question of soft-tissue mass in the pelvis. An elective cesarean section was decided upon and was performed on the following day under general anesthesia.

A low midline incision was made, and the abdomen opened down to the peritoneum. There was a dark-bluish color to the peritoneum, but dissimilar to the usual picture of free blood in the peritoneal cavity. There seemed to be a blood clot attached to the anterior peritoneum, making it difficult to enter the cavity. The incision was extended above the umbilicus, and the same condition encountered.

With the realization for the first time that the structure encountered was placenta and that the fetus was extrauterine, the placenta was broken through (an amniotic sac was then met) and opened, and a female infant weighing 7 pounds, 5 ounces, and normal in every respect, was delivered. The baby cried immediately. A portion of the membranes was adherent to the infant's scalp and had to be peeled off.

The placenta was bleeding freely, and its removal was begun. At this point the anesthetist reported that she could not palpate a pulse. A sternal needle was introduced, and administration of plasma started and a subcutaneous injection of 2000 cc. of physiologic saline solution was begun in the thighs.

The placenta was found to be attached to the major portion of the anterior peritoneal wall, the uterus, both tubes and ovaries, the ileum, the omentum, the sigmoid colon and the cul-de-sac. The size of the uterus was consistent with a 3 months' pregnancy, and it was soft. It was impossible to note if the fallopian tubes were intact. Owing to the placental attachment they were raw and bleeding after its removal.

There was considerable bleeding from many points of placental attachment, and the patient still had no perceptible pulse. Another sternal needle was inserted, and another unit of plasma started.

Bleeding points were ligated, where possible, and Gelfoam was placed against oozing surfaces. The abdomen was closed without drainage. There still was no pulse and the patient was literally gasping for breath. One unit of plasma was now absorbed, and the second was running into the sternum well. Fifty minutes after the operation had been started there was a perceptible pulse (the patient had been pulseless for over 20 minutes).

On the 2d postoperative day the temperature, pulse and respirations were normal, and the patient was ambulatory. Convalescence progressed satisfactorily, and mother and baby were discharged from the hospital on the 12th postoperative day. Six weeks after the operation the mother was in good condition, and the baby showed no abnormalities.

Ovarian pregnancy, though less dramatic than abdominal pregnancy, is of rarer occurrence. Crossen,[10] in a review of the literature, cites Eckerson as stating the ratio of ovarian pregnancies to ectopic tubal gestation to be 1:339. In 1946 Danforth[11] found 70 cases of ovarian pregnancy in the literature. Toplack[12] reviewed the world literature and collected 112 cases of ovarian pregnancy to February, 1950. Culbertson[13] reports a case of simultaneous tubal abortion and intra-uterine pregnancy.

Fejer[14] presents a case of coexisting intra-uterine and abdominal pregnancies with survival of both children and mother. Strumpf[15] reported 1 case of ovarian pregnancy with living mother and child. Novak,[16] in a review of the literature, found 278 cases of intra-abdominal and intra-uterine pregnancy coexisting.

Spiegelberg, in 1879, outlined the following criteria for the diagnosis of ovarian pregnancy: the fallopian tube on the affected side must be intact; the fetal sac must occupy the position of the ovary and must be connected to the uterus by the ligament of the ovary; and definite ovarian tissue must be found within the walls of the sac.

The symptoms of ovarian pregnancy are usually not as obvious as those of rupture in tubal pregnancy, since the pregnancy almost never goes to term, the rupture usually occurring early in gestation; the hemorrhage associated with the rupture is usually slow and not as profuse.

The diagnosis is not often made before operation. The condition is usually diagnosed as rupture in tubal pregnancy, ovarian cyst (ruptured or twisted on its pedicle) or appendicitis.

Mrs. A. P., a 28-year-old woman, was admitted to the Harrington Memorial Hospital on February 4, 1943, at 7:40 a.m. The diagnosis on admission was "perforated appendicitis with abscess."

Twenty-five hours before admission, the patient had been awakened with sharp pain in the right lower quadrant of the abdomen, followed by vomiting. The pain quickly subsided, only to recur in 1 hour and persist, with intermittent vomiting, until admission. The patient had never before been pregnant but had missed the last menstrual period. There had been no vaginal bleeding.

Physical examination disclosed a tender mass in the right lower quadrant. Vaginal examination revealed a soft, closed cervix with no bleeding or discharge. On bimanual examination a slightly enlarged uterus was palpated. The temperature and pulse were normal. The blood pressure was 120/60. The urine was normal, and the white-cell count was 16,500. The preoperative diagnosis was "appendiceal abscess complicating 2 months' pregnancy." The 1st day of the last period had begun on December 3, 1942.

At operation considerable free blood was found in the peritoneal cavity; there were some large clots. The right ovary was indistinguishable from a large, formed clot. The right tube was swollen, but intact. The left tube and ovary were normal. The uterus was enlarged and soft. The appendix was injected.

The whole mass of ovary, clot and right tube was excised. The appendix was removed, and the abdomen was closed without drainage. The patient made an uneventful convalescence.

On pathological examination the specimen consisted of an oval mass of blood clot measuring 9 by 5.5 by 4 cm. It was partially covered by what appeared to be a gray membrane. The tube and ovarian mass measured 7.5 by 6 by 4 cm. in total. It was dark red. There was a sac near one edge 1 cm. in diameter full of clear fluid. No fetus was identified. The appendix was slightly injected.

The pathological diagnoses were ovarian pregnancy, hematosalpinx and chronic appendicitis.

On September 29 the patient was delivered normally of a living female infant.

Summary

Two rare types of extra-uterine pregnancy, successfully handled in a small community hospital, are here reported.

1155 N. W. 14th Street

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CERVICAL CYTOLOGY AS A PRACTICAL SCREENING PROCEDURE FOR CANCER*

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AN EDITORIAL in the *New England Journal of Medicine*[1] calls attention anew to the possible role of the vaginal smear as a technic for population screening for uterine cancer. The editorial, which based its observations on a report emanating from the director of the Division of Cancer of the Massachusetts Department of Public Health, stated: ". . . because of both the expense involved and the relatively few cases discovered on screening . . . it is not feasible for a State Health Department to offer this test on an extensive scale for women without gynecologic symptoms."

The low incidence of positive unsuspected cases and the resulting relatively high cost of the survey prompt some discussion of various pertinent factors. The survey based its conclusions on a single vaginal smear. Greater accuracy has been reported when two smears have been studied. The question of vaginal versus cervical smear or scraping is of vital importance. The cervical technic is much more accurate in revealing preclinical or unsuspected cancer.

Only 3 of 9 unsuspected cancers were detected in the screening program, and greater accuracy might have reversed the conclusion regarding the practicability of the entire procedure.

The editorial referred to above wisely points out that the detection of uterine cancer has varied in different hands from 3 per thousand to 10 per thousand. It further states: "In an unpublished series of 700 women coming to an internist's office, 10 positive smears revealed 7 unsuspected and 2 clinically suspected carcinomas of the cervix, an incidence of unsuspected cases of 1 per cent." This finding is more in keeping with the percentage of unsuspected cancer being revealed in the Cancer Cytology Center of the Dade County Cancer Institute, where 300 physicians are using the cervical cell-scraping test for detection. In a series of 3542 consecutive tests on women attending physicians' offices for various reasons, 61 definitely confirmed cervical cancers were found; 37 were "suspected," as indicated by the clinical findings or by abnormal bleeding or discharge, and 24 (0.68 per cent) were totally "unsuspected."

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As the editorial indicates, the accuracy of cytodiagnosis is dependent upon the interest of the person taking the specimen, the experience and intellectual quality of those making the cytodiagnosis and the type of case studied. It points out that advanced and clinical cases of cervical cancer should not be included in a screening program since the lesion is clinically evident and since biopsy is clearly indicated in the presence of abnormal bleeding.

A repeat test should be taken in all cases of questionable smears. The editorial states — "Had these (repeat) tests been taken, a more favorable report as to the diagnostic value of this smear might have resulted." It is noteworthy that the number of questionable smears may be minimized by the direct cervical smear or cell-scraping technic,[2] thus reducing the number of smears to be repeated.

There are those who would question the admission that large-scale screening is impracticable because of the low yield reported in Dr. Lombard's valuable study. Many other groups screened have shown a yield of 1 per cent or more. The increased yield would therefore mean a significant reduction in the cost of case finding, and the figure of $1,700 per case seems out of line in view of other estimates of the cost of screening. Nieburgs,[3] in Georgia, estimates the cost at $150. Dr. Joe V. Meigs has estimated the cost to be $900. In the Cancer Cytology Center at the Dade County Cancer Institute the cost of finding an unsuspected case of cancer of the cervix approximates $300.

The editorial further states:

> It may be some time before an adequate number of technicians and pathologists trained in cytologic diagnosis will be available. Until then, screening will have to be confined to those clinics and private physicians who have at their disposal reliable cytologic laboratory assistants.

To one who has participated actively in the field of cytology for more than ten years, it seems that the cancer organizations have not sufficiently emphasized the usefulness of cytology and that the training programs for both technicians and cytologists have not been adequately encouraged. With proper sponsorship and adequate reward, scores of technicians could be trained in special cytology centers set up for training within a twelve-month period.

Although it may not yet be feasible or financially justifiable, as stated in the report, to undertake large-scale screening at the state level, it appears that steps should be taken to set up cytology centers where active training of technicians, pathologists and cytologists would be emphasized. At the same time, physicians should be advised through an active educational campaign to utilize the test on a more widespread basis as part of the annual health examination as a continuing effort to improve cancer control. The program of the Cancer Cytology Center of the Dade County Cancer Institute commands evaluation in this respect.

It should be pointed out that statements made in Dr. Lombard's report regarding the accuracy of a single vaginal smear do not eliminate the practicability of other cytologic methods. In preclinical (unsuspected) cancer of the cervix, a single vaginal smear may be compared to the cervical cell-scraping as a single punch biopsy compares to the "ring-biopsy" histologic technic.[4]

TABLE 1. *Results of Cytologic Tests for Uterine Cancer.*

Author	Cases of Early Cancer	Cytologic Technic		
		Positive vaginal smear	Positive cervical smear	Positive cervical scraping
Foote and Li[5]	18	9 (False-negative tests, 50%)	14 (False-negative tests, 22%)	—
Kulcsar[6]	20 (100 specimens)	55 (False-negative tests, 45%)	—	93 (False-negative tests, 7%)
Achenbach et al.[7]	60	45 (False-negative tests, 25%)	—	—
Reagan[8]	54 (82 specimens)	—	43 (False-negative tests, 20%) 62 (False-negative tests, 24%)	50 (False-negative tests, 7%) 77 (False-negative tests, 6%)

Various cytologic technics have been used in different screening programs, and this may have influenced the number of positive cell findings, especially in the early stages (Table 1). If carcinoma in situ may be taken as a common form of "early" cervical cancer, the experiences of various investigators reflect the variability of positive cell findings with different technics.

Foote and Li,[5] studying 18 proved cases of carcinoma in situ, diagnosed positive smears in 14 smears of the cervical canal, whereas they found positive cells in only 9 vaginal-smear specimens. Kulcsar,[6] using the surface cell-biopsy method, was able to detect cancer cells in 93 of 100 specimens obtained from 20 patients with early cancer; the cellular content of the vaginal pool (vaginal smears) contained neoplastic cells in only 55 of 100 specimens. Achenbach, Johnstone and Hertig[7] identified 45 of 60 proved cases of carcinoma *in situ* when the cellular content was collected from the vaginal pool. More recently, Reagan[8] reported that scraping of the uterine cervix disclosed anaplastic cells in 50 of 54 patients with carcinoma *in situ* and in 77 of the 82 specimens. Material aspirated from the cervical canal showed tumor cells in only 43 of the 54 patients and in 62 of the 82 specimens.

In an active campaign of professional and public education, sponsored by the Dade County Medical Association, over 300 physicians of Dade County

are performing cervical cytology tests with increasing frequency, many on a routine basis in response to a demand on the part of the patient.

The results appear highly gratifying from the standpoint of the number of unsuspected cancers found and the resultant low cost per case. Although the use of the vaginal smear in a state department of health may not be practicable, as concluded in Dr. Lombard's report, it seems unwise to dismiss other cytologic procedures without trial. Cervical cytotests as a screening procedure in the family physician's office are yielding brilliant results in several centers. The family physician's office is the logical cancer-detection clinic today, and with the widespread use of cytology, it is the conviction of many that the ultimate potential of this system of cancer detection and control is far beyond present expectations.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

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CASE 38361

Presentation of Case

First admission. A seventy-two-year-old woman entered the hospital because of cough.

The patient had noted increasing cough for three or four months prior to entry. She had had a history of bronchitis for at least fifteen years, with a cough that had become worse recently, with the production of yellowish-green sputum, about a quarter to half a cupful daily, but she had had no chills or fever. During the few weeks before entry the cough had also been associated with nagging pain in the right middle portion of the abdomen. Her appetite had been poor, and there had been a weight loss of 12 pounds. Her physician detected a rapid pulse, a right pleural effusion and an enlarged liver but thought that the effusion had subsided on bed rest. For several years she was known to have had an enlarged heart associated with a systolic murmur, and she had been on moderate salt restriction.

X-ray examination of the chest seven years before admission showed bright lung fields, with both leaves of the diaphragm low in position and somewhat prominent pulmonary markings throughout; there were no definite areas of parenchymal infiltration, but in the right fourth and fifth interspaces anteriorly in the region of the middle lobe there was a collection of prominent markings, with several areas that had the appearance of cyst-like cavities suggestive of bronchiectasis; the heart was centrally hung, and the right side seemed to be slightly more prominent than usual. The patient had had a radical mastectomy on the left at another hospital eight years prior to entry; the tumor removed was diagnosed by the pathologist as carcinoma simplex, with no lymph-node metastases.

Physical examination revealed a thin, emaciated, alert woman in no distress. She weighed 83 pounds. A scar of the left radical mastectomy was present. The chest was hyperresonant throughout except for the right base, in which there were dullness, diminished breath sounds and râles. Anteriorly, there was dullness below the fourth rib, with inspiratory râles. The heart had a Grade III, apical systolic murmur; the pulmonic second sound was slightly louder than the aortic. The liver was thought to be palpable, and the liver area was tender. There was no edema.

The temperature was 99.8°F., the pulse 92, and the respirations 28. The blood pressure was 135 systolic, 70 diastolic.

The urine had a specific gravity of 1.014 and was normal. Examination of the blood revealed a hemoglobin of 14.4 gm., and a white-cell count of 14,100, with 88 per cent neutrophils, 9 per cent lymphocytes, 1 per cent monocytes and 2 per cent eosinophils. The nonprotein nitrogen was 14 mg., and the total protein 6.8 gm. per 100 cc., with an albumin-globulin ratio of 1.4. A stool was guaiac negative. The sputum was negative for acid-fast organisms. A roentgenogram of the chest showed a moderate amount of fluid in the right pleural space; the visualized lung fields were rather bright, and

there was diffuse fine scarring in both lungs, the greatest changes being in the right. The heart shadow was probably slightly enlarged, without characteristic configuration. Definite evidence of metastases was not seen. The bones of the skull, lumbar spine and pelvis revealed no definite metastasis. A barium-enema examination demonstrated an extremely redundant colon, without constant filling defect or ulceration. A gastrointestinal series was negative except for a small hiatus hernia, which emptied readily.

An electrocardiogram showed a sinus tachycardia at a rate of 110, a PR interval equal to 0.15

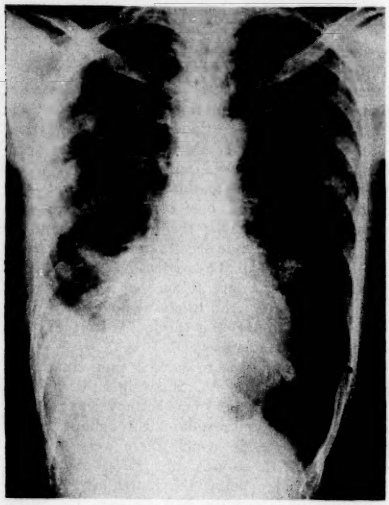

FIGURE 1. *Roentgenogram of the Chest.*
Arrow points to the portion of the heart that did not move normally during fluoroscopic observation.

second and a QS deflection of low voltage in Leads 1 and AVL. The T waves were upright in Leads 2, 3, AVF, V_2, V_3, V_4, V_5 and V_6, low and upright in Lead 1, flat in Lead AVL and inverted in Lead V_1. The P waves were rather prominent in Leads 2 and 3. The R waves were present in Lead V_1. An old, high, lateral myocardial infarction was considered possible. An electrocardiogram repeated three days later was similar. The prominent P waves in Leads 2 and 3 suggested the presence of hypertrophy of the right ventricle.

Thoracentesis on the right side was performed two days after admission; 250 cc. of dark-red fluid was withdrawn, which had a specific gravity of 1.014 and contained 28,000 red cells and 5880 white cells per cubic millimeter, with 20 neutrophils, 5850 lymphocytes and 10 monocytes. Thoracenteses repeated five and seven days later yielded 50 and 70 cc. of yellowish-red fluid respectively from both sides. The culture of fluids revealed no growth, and the cytologic reports were unsatisfactory or doubtful. On the third hospital day, the patient started to have pain in the left side of the chest, and pleural rubs and coarse rales were heard in the left third interspace anteriorly, which lasted for only one day. On the tenth day, the x-ray examination of the chest was repeated (Fig. 1); the lungs showed no appreciable change, the fluid persisted in the right pleural space, and in the right lower portion of the lung field near the fluid, there was a convex density; the left border of the heart, near the apex, appeared unusually prominent, and under fluoroscopy, there appeared to be a definite convexity on the anterior aspect of the left ventricle, which did not show normal contraction. An electrocardiogram two days later gave no indication of myocardial infarction. On the twelfth day exploration of both common femoral veins revealed no abnormality, and the veins were ligated. The patient was given penicillin and other supportive measures, with only slight improvement. She was discharged at her request on the twenty-fourth hospital day.

Final admission (three months later). One month after discharge from the hospital her physician found much fluid in the right side of the chest and that the patient was breathing essentially only with the left lung. A few days prior to admission her physician noted that the aeration of the right middle and lower portions of the chest seemed better. She had been given chloral hydrate and pentobarbital sodium (Nembutal) for sleep, without much effect, and the night before admission she told her husband that she was going to take more until she did get to sleep. On the morning of admission she was found to be unresponsive except to strong stimuli.

Physical examination revealed that she was drowsy and confused but talking spontaneously and moving about in bed. There was cyanosis of the hands and toes. The heart did not appear to be enlarged, and no murmurs were heard. The aortic second sound was less than the pulmonic. There was dullness and diminished to absent breath sounds in the lower half of the right-lung field. The liver was thought to be palpable, and the edge was tender.

The temperature was 101°F., the pulse 140, and the respirations varied from 20 to as low as 10 on one occasion. The blood pressure was 70 systolic, 55 diastolic.

The urine was positive for barbiturates, had a specific gravity of 1.026 and gave a ++ reaction for albumin; the sediment contained 100 red cells and 25 white cells per high-power field. The hemoglobin was 13 gm. per 100 cc., and the white-cell count 13,500, with 93 per cent neutrophils. A

roentgenogram of the chest showed an increase in the fluid in the right pleural cavity (Fig. 2). The right lower lobe was reduced in size, with patchy areas of increased density within it. The pleura at the right base was nodular. A small patch of increased density, approximately 2 cm. in diameter, was apparently within the anterior segment of the right upper lobe. The left lung was emphysematous. The heart was definitely enlarged.

The patient remained confused although improving generally. On the third day a rapid auricular fibrillation at a ventricular rate of 140 associated with respiratory distress and cyanosis developed. She seemed to improve under digitoxin therapy and oxygen. However, she was found to be more disoriented the next morning, although the ventricular rate decreased to about 110 per minute, and respiration was easier. She died on the fifth hospital day.

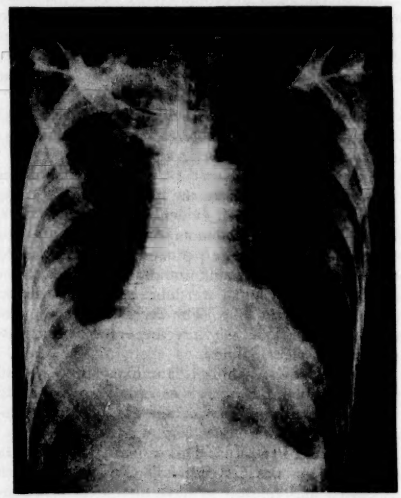

FIGURE 2. *Roentgenogram of the Chest.*

DIFFERENTIAL DIAGNOSIS

DR. LEWIS KANE*: "She weighed 83 pounds." The record does not give her height.

DR. BRIANT L. DECKER: The patient was moderately emaciated; she was 5 feet, 6 inches in height.

DR. KANE: The only thing that is clear to me is that the patient must have been seriously ill and further that her illness was probably due to a number of diseases. She had heart disease and chronic disease of the lungs, and an adenocarcinoma of the breast had been removed eight years prior to entry. Throughout the entire history I am reminded constantly that she had heart disease. However, the information seems to be conflicting. On a number of occasions the heart is recorded as being normal in size and at other times as being slightly enlarged. Perhaps I had better see the x-ray films.

DR. JOHN L. SOSMAN: We no longer have the x-ray films taken seven years before admission. In the films taken during the first admission the findings are all essentially as described in the physical examination: fluid in the right base and a heart enlarged to the left (Fig. 1). Although this heart would not be enlarged for a 165-pound man, for an 85-pound woman of narrow dimensions, I believe it is enlarged; also, the diaphragm is very low. It is hard to determine whether the heart is enlarged to the right because of the mass within the thorax. The size of the heart has not changed on any of the examinations until the final examination, on which, in spite of its being an anteroposterior film taken in the supine position, the heart shows a significant enlargement demonstrated by the extremely small margin on the left between the lateral border of the heart and the rib cage (Fig. 2).

DR KANE: Is there any evidence of congestive heart failure?

DR. SOSMAN: Not until the final examination, when the vessels appear more prominent than normal. The left ventricle has a sharply rounded contour; I think this is present in all examinations here but is shown best in the right anterior oblique film. There is a sharp nodule about the size of half a golf ball or somewhat larger projecting out there. This is the area at the apex that did not contract normally during fluoroscopy.

DR. KANE: That is anterior to the left ventricle.

DR. SOSMAN: Yes; in its anterolateral aspect.

DR. KANE: May I see the electrocardiograms now?

DR. EDWIN O. WHEELER: The electrocardiogram taken at the time of the first admission shows small R waves and prominent S waves in Lead 1 and small R waves in Lead V_1. In some tracings there appears to be a QS complex in Leads 1 and AVL. In the electrocardiogram at the time of the second admission there had been no significant change. The electrocardiograms were unusual and raised the question of high lateral myocardial infarction, incomplete right-bundle-branch block and hypertrophy of the right ventricle.

DR. KANE: It seems apparent that this woman had a certain degree of coronary-artery disease and congestive heart failure, but I do not think it was responsible for the events that led to her admission to the hospital and to her subsequent death. The enlargement anterior to the heart that Dr. Sosman pointed out could represent an aneurysm of the myocardium as the result of an

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infarct that occurred some time previously. It certainly was not a recent occurrence as implied in the history but apparently went back to the first x-ray film. A primary tumor of the myocardium is a possibility, but I shall only mention it in passing. A metastasis to the pericardium is also a possibility, and I shall discuss that later.

The major difficulty seems to have been within the lungs. The patient had a history of bronchitis for fifteen years and a cough that became worse shortly before admission. A series of chest films showed rapid and progressive change; the first one demonstrated fluid in the right pleural cavity and a diffuse scarring of the lungs. Paracentesis showed that the fluid contained hemoglobin. On the third hospital day the patient had a sudden pain in the left side of the chest that apparently lasted for only one day, and on the tenth day the femoral veins were explored and ligated — probably in the hope rather than the expectation that the source of the difficulty would be elucidated and eliminated. I cannot exclude the possibility of multiple pulmonary emboli, but I do not think they were responsible for her death. There is no reason to invoke an endocarditis of the right side of the heart as being a source of multiple pulmonary emboli.

My opinion is that something was going on for a long time prior to admission to the hospital. We are told that the patient had anorexia, pain in the right midportion of the abdomen, a 12-pound weight loss and effusion on the right without prior pain in the chest. These findings suggest the possibility of a neoplasm. I cannot rule out a primary neoplasm of the lung, but I cannot find evidence to support such a diagnosis. There was no cytologic examination of the sputum, no enlargement of lymph nodes or any other supportive evidence. On the other hand, we do know that eight years before entry she had the left breast removed for carcinoma. Metastases from carcinoma of the breast have been known to occur as late as twenty years after the removal of the primary lesion. The failure of metastases to show in the x-ray film perhaps Dr. Sosman can explain.

DR. SOSMAN: I do not think one can say there was a failure to show metastases; I think it is rather a failure to be able to put a finger on any of those shadows and say they are definitely cancer. In the films there is a fairly constant round shadow more to the front of the chest at the right base. On the last examination there is a suggestion of mottling along the pleura in addition to what was previously noted. Some of this could be fibrin in the bloody pleural fluid, but it could equally well be tumor nodules. There is a lesion there that at first was dismissed as being the type found in generalized chronic lung disease, but by the time of the last examination, the mass had reached fairly large proportions. There is also a nodule on the left, which is present in the various films. Although I cannot rule out, as Dr. Kane did, that these represent infarctions, I think there is definite evidence of disease in the chest over and above what was described in the old examination seven years previously. These old findings are present on the right: the fibrous markings, the emphysema and some suggestion of a cavity of bronchiectasis. There is definite decrease in size and a fair degree of collapse of the right lower lobe.

The gastrointestinal series, which is essentially normal when considered together with the barium-enema examination, shows lower-bowel encroachment in the right upper quadrant. In a plain film of the abdomen, although the visceral shadows are not well demarcated, possibly owing to the lack of fat, there is good indication of a large liver. The metastatic series of bone, including spine and pelvis, was negative.

DR. KANE: You have helped me a great deal. I think there is much more to see in the films than the protocol led me to believe.

In view of the history of a carcinoma of the breast eight years before the patient came into the hospital and the added evidence in the x-ray films, I favor metastatic carcinoma of the breast to the lungs, the liver and the pericardium to explain the mass seen in the x-ray film, and also perhaps to the mucosa of the right-lower-lobe bronchus, causing atelectasis of that lobe. The decrease in volume of the right lower lobe may have been due to compression by the pleural fluid.

DR. WHEELER: I think it is unlikely that she had a myocardial infarct large enough to give her an aneurysm without more definite electrocardiographic evidence.

DR. MYLES P. BAKER: This woman, when she was discharged on the first admission, was very much depressed and refused to have any medical attention. I was called in during the last two months because her daughter became much concerned, and persuaded her to see a doctor. I was impressed by the immobility and retraction of the right chest and by the fact that she was breathing almost entirely with the left lung. It did not look like a chest full of fluid but more like lower-lobe collapse, possibly with some fluid. I have never seen this retracted chest wall with diminished aeration of the lungs, except with carcinoma or lymphoma. I obtained one sputum for cytologic examination, which was negative, and then we restricted our conversation to ornithology. I gave her small amounts of medication at the time, but I did not clear out the medicine closet. The barbiturate poisoning was very well handled by the staff in the emergency ward, and I thought we had corrected that. Then she again lapsed into stupor, with cardiac arrhythmia. The pericardial friction rub that developed in the last twenty-four hours gave rise to the question of whether she had a painless myocardial infarction, but I considered metastatic

disease involving the pericardium much more likely.

DR. DECKER: I had taken care of the patient for ten years; she had a cough all those years. She was always thin and never weighed more than 92 pounds. When she entered the hospital she weighed 85 pounds. The first time, I thought she had either metastatic disease or congestive heart failure. I believed after the studies that she was not in congestive heart failure. While I was away for a week-end and Dr. Arthur S. Pier, Jr., was taking care of her, she had an attack of pleurisy on the left with friction rub. We could see nothing in the x-ray films at that time. It was Dr. Pier's suggestion that perhaps this was pulmonary infarction, although it seemed a long time to retain a pleural effusion resulting from pulmonary infarction at the right base. When I first found the effusion at the right base she refused hospitalization. It was not until she became much more short of breath and uncomfortable that she did go into the hospital. The veins were tied in the hope that she possibly had infarction in the lungs, but it was believed that metastatic disease was more likely.

After discharge she went to a hotel and refused to see anyone. Against her wishes, I telephoned her frequently. I had not given her any medication since she left the hospital though previously she had been taking 15 mg. of phenobarbital and I assume that she had kept a supply. When she was in the hospital, she became quite disoriented; we took away all medications, — chloral hydrate, barbital and so on, — but the disorientation cleared only slightly. She was still disoriented, very forgetful and very hostile when she was discharged. It would not surprise me if she had metastatic disease of the brain although at the time we thought her mental condition was due to arteriosclerosis.

CLINICAL DIAGNOSIS

Metastatic carcinoma of lungs from carcinoma of the breast.

DR. KANE'S DIAGNOSIS

Metastatic carcinoma from breast to lungs, liver and pericardium.

ANATOMICAL DIAGNOSES

Metastatic carcinoma of pleura, from carcinoma of breast.
Hydrothorax.
Hydropericardium.
Pulmonary emphysema.
Rheumatic endocarditis, chronic, of mitral valve, with insufficiency.

PATHOLOGICAL DISCUSSION

DR. ROBERT H. FENNELL, JR.: The principal finding at autopsy was in the right side of the chest. The right lung was encased in a thick white mass, which formed a complete ring around the right lung and varied in thickness from 0.5 to 1 cm. Grossly, we thought the process was fairly typical of a mesothelioma. Microscopically, the tumor was an adenocarcinoma perfectly compatible with origin from the breast. No tumor was found elsewhere. The right lung was atelectatic; the left was emphysematous. This patient had approximately 400 cc. of fluid in the left pleural cavity and approximately half that amount in the pericardial cavity. The liver, though not enlarged, showed microscopically a fairly typical central congestion that one sees with congestive heart failure.

A PHYSICIAN: Was there cancer in the liver?

DR. FENNELL: No; and the liver was not enlarged. It weighed only 1000 gm., but it was down to the iliac crest at autopsy.

DR. WHEELER: What was the heart disease?

DR. FENNELL: The heart was slightly hypertrophied; there was some old rheumatic endocarditis, with definite shortening and thickening of the anterior cusp of the mitral valve — enough to have produced a moderate degree of insufficiency. There was a fibrinous pericarditis, which explains the friction rub heard, but there is no ready explanation of the pericarditis. It was similar to the type seen with uremia, but there were no changes in the kidney to suggest it. No metastatic tumor was present in the pericardium.

DR. KANE: What was the mass described as being anterior to the left ventricle?

DR. FENNELL: There was no mass. The heart may have been pushed over to the left by the massive right pleura.

DR. KANE: Was there any evidence of a pulmonary infarction on the left where the rub was heard.

DR. FENNELL: No.

CASE 38362

PRESENTATION OF CASE

First admission. A fifty-three-year-old man was admitted to the hospital because of shortness of breath.

Ten years prior to entry the patient had an episode of severe chest pain, for which he spent ten weeks in bed; he was told that he had a "coronary." After this he had occasional episodes of precordial pain and occasional cramps in the left leg, both of which followed exertion. Three years prior to admission he first noted exertional dyspnea. He was given aminophylline pills and later digitalis, with some improvement; the digitalis was stopped six months prior to entry. During the six months before admission he gradually lost energy and "drive," became moderately anorexic and complained of a growing epigastric pain. Three weeks before admission his dyspnea became more severe, and orthopnea, ankle edema and a depression in the urinary output were subsequently noted.

The patient had had a chronic nonproductive cough for many years. There had not been any nausea, vomiting, hemoptysis, change in bowel habits or urinary symptoms. There was no history of hypertension or rheumatic fever. His father had died of heart disease at the age of forty.

Physical examination revealed a chronically ill man with obvious respiratory distress. The neck veins were distended. Scattered rales were heard at the bases of the lungs posteriorly. The heart was enlarged, with the apical beat palpated 14 cm. from the midsternal line in the sixth intercostal space. There was a Grade II, blowing, apical, systolic murmur and a marked apical diastolic gallop; the aortic second sound was equal in intensity to the pulmonic. An enlarged, smooth liver was palpated, the edge being 2 cm. below the costal margin. There was mild sacral and ankle edema.

The temperature was 98.6°F., the pulse 120, and the respirations 30. The blood pressure was 120 systolic, 95 diastolic.

The urine had a specific gravity of 1.024 and was normal. Examination of the blood revealed a hemoglobin of 13.4 gm. and a white-cell count of 10,700, with 36 per cent neutrophils. The sodium was 130 milliequiv., the chloride 95 milliequiv., the potassium 4.8 milliequiv. and the carbon dioxide 26.6 milliequiv. per liter; the nonprotein nitrogen was 30 mg., the total protein 5.72 gm., with a normal albumin-globulin ratio, the thymol turbidity 0.8 units, the alkaline phosphatase 4.2 units and the serum cholesterol 216 mg. per 100 cc. A blood Hinton test was negative. Roentgenograms of the chest demonstrated generalized cardiac enlargement involving both the right and left ventricles, a tortuous, somewhat sclerotic aorta and accentuation of the vascular markings in the lungs. An electrocardiogram showed a normal sinus rhythm at a rate of 100, a PR interval of 0.14 second, QRS interval of 0.17 second and left-bundle-branch block. The T waves were low and upright in Lead 1 and upright in Leads 2, 3 and AVF; the R waves were small in Leads V_1, V_2, V_3 and V_4 and broad and slurred in Lead V_6; the S waves were broad in Leads V_1, V_2 and V_3.

Treatment with digitoxin, mercurial diuretics, aminophylline, low-salt diet and ammonium chloride resulted in a diuresis and considerable improvement in the dyspnea. On the fourth day the patient felt a dull aching, nonpleuritic-type pain in the right upper anterior part of the chest, and coughed up dark-red blood. This was followed several hours later by a severe precordial pain, accentuated by respiration; a pleural friction rub was found 5 cm. below the left nipple. Roentgenograms of the chest and the electrocardiogram were unchanged. Dicumarol was added to the treatment. He recovered from the episode of pain quite rapidly. He continued, however, to have occasional episodes of pain in the precordium and anterior portion of the chest of brief duration, with radiation to the left shoulder, and occasional attacks of paroxysmal nocturnal dyspnea. He was discharged after a month only slightly improved; he had been able to remain out of bed in a chair for only short intervals.

Final admission (two weeks later because of abdominal pain). In the interval the patient had done fairly well at home on a bed-to-chair regimen; he had not had any respiratory difficulty or chest pain, although he had had to sleep at a 30° angle. Three days prior to entry pain and tenderness in the left lower quadrant of the abdomen suddenly developed. The pain persisted and on the following day involved the left flank and testicle. The pain gradually decreased in intensity, being almost completely absent on the morning of admission, when the left-lower-quadrant pain returned and was associated particularly with changes in position. During this three-day period the dyspnea, paroxysmal nocturnal dyspnea and precordial distress returned. There had not been any vomiting, diarrhea or constipation. He had not had any urinary symptoms except for a decrease in urinary output during the three-day period; urinalysis had been negative until the day of admission, when it showed 15 to 20 red cells per high-power field in the sediment.

Physical examination revealed a pale man who was sweating slightly and who complained of pain in the lower abdomen when he moved. The neck veins were distended. The lungs were clear. Examination of the heart was unchanged from the previous admission. A nontender liver edge was palpated four fingerbreadths below the costal margin. There were no other palpable organs or masses in the abdomen and no areas of tenderness. There was no costovertebral-angle tenderness. The femoral, popliteal and posterior tibial arteries could not be felt on either side. The right leg appeared somewhat duskier than the left, but the temperature seemed to be the same in each.

The temperature was 100.6°F., the pulse 120, and the respirations 22. The blood pressure was 110 systolic, 100 diastolic.

The patient was apprehensive, lethargic and occasionally incoherent. He complained of pain on both sides of the lumbar spine. Ten hours after admission the skin showed mottled cyanosis from the waist down, and the legs were colder than the arms. He became unresponsive, and died fourteen hours after admission.

Differential Diagnosis

Dr. Francis G. Barnum, Jr.*: This is the case of a fifty-three-year-old man who had heart disease and developed congestive failure; then a complication ensued that probably caused his death. There are two fundamental questions to be answered:

*Assistant in medicine, Massachusetts General Hospital.

What type of heart disease did he have, and what was the nature of the final episode?

Atherosclerosis of the coronary vessels is the most probable cause of this patient's heart disease for a number of reasons. In the first place, he had an episode of severe chest pain ten years before admission, which kept him in bed for ten weeks and which was called a "coronary"; presumably, this was a myocardial infarction. Secondly, he subsequently had occasional episodes of precordial pain related to exertion; angina often makes its first appearance after myocardial infarction. Thirdly, he had occasional cramps in the left leg after exertion, suggesting that the atherosclerosis was not limited to the coronary vessels. Fourthly, his father had died of heart disease at the age of forty; this is not conclusive, of course, but in patients with angina pectoris one often uses as a prognostic yardstick the age of death of the parents, if they had coronary-artery disease. Fifthly, the only murmur heard on examination was an apical systolic murmur; this, as the only murmur in the presence of a heart as large as this, was undoubtedly due to cardiac dilatation with relative mitral insufficiency. It is logical that this dilatation was due to weakening of the myocardium from coronary atherosclerosis and the previous myocardial infarction. Sixthly, an electrocardiogram showed left-bundle-branch block, which is most often due to coronary-artery disease. Finally, an apical diastolic gallop is common in dilatation of the left ventricle as well as in left-bundle-branch block.

Other causes of heart disease can be fairly readily excluded. Rheumatic heart disease with mitral insufficiency alone can be excluded on the basis of the absence of history of rheumatic fever and the fact that mitral insufficiency alone would not have produced this degree of cardiac enlargement. Syphilitic heart disease can be excluded by the negative Hinton test and the absence of an aortic murmur. There was nothing to support the diagnosis of myxedema or of beriberi heart disease. Congenital heart disease can be excluded by the location and intensity of the murmur, for the only form of congenital heart disease that produces an apical systolic murmur near the apex — namely, ventricular septal defect — would produce a loud murmur and thrill; also the murmur in this condition is usually maximal at the fourth left interspace next to the sternum, not at the apex.

Among the rarer causes of heart disease one might consider cardiac amyloidosis; however, there was nothing in the history or physical examination to suggest this diagnosis. The same statement can be made of the collagen diseases. Myocardial sarcoidosis is another possibility, but there were no cutaneous lesions or lymphadenopathy and the globulin was normal.

We have, then, this man with arteriosclerotic heart disease who probably had a myocardial infarction at the age of forty-three and who began to have exertional dyspnea three years before his first admission. Digitalis was given, with some improvement, as might have been expected. The fact that it was stopped and he grew worse confirms the impression that his heart was failing. The anorexia and loss of energy are consistent with beginning congestive heart failure. Nothing is said about the character of the epigastric pain so I must assume that it was due to poor functioning of the gastrointestinal tract caused by edema.

Three weeks before admission the gradual myocardial failure became more acute, with orthopnea, ankle edema and a depression in the urinary output; the last was probably due to the accumulation of edema fluid in the tissues that would normally be excreted in the urine. An outside possibility that the gnawing epigastric pain had been treated with Banthine and that this had caused a depression in the urinary output is unlikely since he had no true urinary symptoms — that is, no true retention.

On examination, the distention of the neck veins, the enlarged liver and the sacral and ankle edema show that the right side of the heart was failing, and the dyspnea and basal rales along with the accentuation of the vascular markings in the lungs show that the left ventricle was also failing. The chemical studies were consistent with congestive heart failure, all values being normal except for a low sodium and chloride. The moderate elevation of the white-cell count is also consistent, but I cannot explain the low percentage of neutrophils. The electrocardiogram showed left-bundle-branch block; the upright T waves in Lead 1 are unusual in left-bundle-branch block and suggest the possibility of a previous myocardial infarction.

On the fourth hospital day the patient felt a dull aching pain in the right upper anterior part of the chest and coughed up dark-red blood. This is perfectly typical of one of the common complications of heart failure — namely, pulmonary embolism. Several hours later a severe precordial pain, with a pleural friction rub 5 cm. below the left nipple, developed. This may have been due to another pulmonary embolus, though it is most unusual for a friction rub to develop so rapidly. The fact that the pain was accentuated by respiration, however, is in favor of a pulmonary embolus.

May I see the x-ray films?

Dr. Stanley M. Wyman: These two sets of films of the chest, taken three days apart, both show considerable cardiac enlargement, which probably involves both left and right ventricles primarily. The aorta is calcified and somewhat tortuous. The enlargement of the hilar and pulmonary vascular shadows is fairly marked and is seen on both examinations. In addition, on the second examination, there is a hazy density in the left-lung field overlying the heart border.

DR. BARNUM: Is there any evidence of beginning dissection of the aorta, such as a wide supracardiac shadow?

DR. WYMAN: No. The aorta is well seen through the heart on both posteroanterior films and is fairly well seen in its upper portion on the lateral films.

DR. BARNUM: I, thus, have confirmation of the embolus to the left-lung field. The most likely source for this embolus is the leg veins. A cardiac source is probably excluded by the absence of auricular fibrillation and of bacterial endocarditis (since rheumatic heart disease and congenital heart disease have been ruled out). Embolus from a mural thrombus in the right ventricle is an outside possibility.

The patient entered the hospital for a second time because of a three-day history of pain and tenderness in the left lower quadrant of the abdomen. That this pain was due to involvement of the kidney is strongly suggested by the radiation to the left flank and testicle and by the fact that urinalysis showed 15 to 20 red cells per high-power field in the sediment. The absence of costovertebral-angle tenderness does not exclude renal involvement.

Could this have been intraperitoneal disease involving the kidney? Pain in the abdomen on motion and with change in position suggests irritation of the parietal peritoneum; however, the fact that the abdomen was not tender makes this unlikely. It is possible that this pain was partly due to occlusion of the superior mesenteric vessels. With the findings given, however, there is not sufficient evidence to make this diagnosis.

The decrease in urinary output was probably caused by a further accumulation of edema. The combination of clear lungs and distended neck veins may have been due to a large component of right-sided heart failure; it may be that the patient was in severe pain and held himself rigidly, thus increasing his intrathoracic pressure and causing distended neck veins; or, finally, pulmonary edema may have been present without audible rales. The blood pressure showed a narrow pulse pressure with a high diastolic pressure, the latter probably due to the excitement and pain of his illness. Dr. Fennell has been kind enough to give me all the blood-pressure values in the two admissions; these were uniformly in the normal range.

The final accident was characterized by lethargy, pain on both sides of the lumbar spine, cyanosis from the waist down and decreased temperature in the legs. This must have been due to a vascular accident involving the lower limbs. The suddenness of onset, with absent pulsations in the leg arteries, is strongly suggestive of an arterial occlusion. Localized thrombosis does not fit the clinical picture, and there is nothing to suggest it; I am therefore left with the possibility of dissecting aneurysm or of multiple emboli.

This patient's pain was consistent with dissecting aneurysm since it waxed and waned and was extremely severe when it was present. The episodes of precordial pain with radiation to the left shoulder may have represented further dissection. The lethargy and incoherence are mental symptoms that can be associated with dissecting aneurysm, presumably because of partial obstruction of the carotid arteries. Pain on both sides of the lumbar spine may have been due to dissection near the aortic bifurcation.

The main argument against dissecting aneurysm is the absence of hypertension both by history and on examination. Additional points against the diagnosis are absence of sudden pain in the chest and back, absence of a basal diastolic murmur and of a characteristic x-ray picture. In the series of cases of dissecting aneurysm of the aorta reported from the Massachusetts General Hospital* evidence of hypertension was found in all. In addition, a typical history with a basal diastolic murmur was found in a significant percentage.

In favor of embolism is the fact that the patient had coronary-artery disease with a probable myocardial infarction ten years before his first admission. It is possible that he had a mural thrombus at that time and that, when congestive failure occurred, more thrombus developed and became a source for emboli. On the other hand, he may have had a silent myocardial infarction sometime after the first admission. It is also possible that any one of the attacks of pain in the chest after discharge represented a myocardial infarct. Electrocardiographic proof of these could not be obtained in the presence of left-bundle-branch block.

The symptoms during the final admission could have been due to embolus to the left renal artery arising in a mural thrombus in the left ventricle,

*David, P., McPeak, E. M., Vina-Solas, E., and White, P. Dissecting aneurysm of aorta. *Ann. Int. Med.* 27:405-419, 1947.

followed by a large saddle embolus or two smaller emboli occluding the iliac arteries. Other possible sources for emboli are a fibrillating auricle and bacterial growths superimposed on a defect of the ventricular septum or rheumatic heart disease. These have already been excluded. Paradoxical embolization via an unsuspected defect of the auricular septum seems far-fetched, as does a source in one of the pulmonary infarcts.

My diagnosis, therefore, is arteriosclerotic heart disease with myocardial infarction, old, and probably recent, with a mural thrombus and emboli to the left renal and to both iliac arteries; the last may have been a saddle embolus. There is a possibility of embolization to the superior mesenteric artery. There were also at least two pulmonary emboli.

Clinical Diagnoses

Coronary-artery disease.
Saddle embolus of aorta, with thrombosis of renal arteries.

Dr. Barnum's Diagnoses

Arteriosclerotic heart disease.
Myocardial infarction, old and recent with mural thrombi.
Emboli to renal and both iliac arteries.
Pulmonary emboli.

Anatomical Diagnoses

Thrombosis of abdominal aorta, with occlusion of renal and iliac arteries.
Renal infarction, left.
Coronary-artery and probably hypertensive heart disease.
Myocardial fibrosis and old infarction.

Pathological Discussion

Dr. Robert H. Fennell, Jr.: The aorta was occluded by a thrombus from the bifurcation to just above the level of the renal arteries. The aorta was dilated above the bifurcation, and in that region the thrombus was yellow and firmly adherent, and appeared older than the thrombus that extended to occlude the renal arteries. Elsewhere in the abdominal aorta there was severe arteriosclerosis. The left kidney was infarcted, but the right was only congested. The heart was huge, weighing 750 gm. There was a scarred area in the posterior part of the interventricular septum. Elsewhere there was patchy fibrosis. The right coronary artery contained an old thrombus, but all branches were severely narrowed and sclerotic. Although it is well known that cardiac hypertrophy may occur in coronary-artery disease, I believe there must have been some other factor to account for the degree of hypertrophy represented by a heart weighing 750 gm. The diastolic pressure of 100 in the presence of cardiac failure indicates that this patient had probably had hypertension in the past. The lungs were emphysematous and slightly edematous.

The appearance of the thrombus in the aorta suggests that it arose there and extended retrogradely to occlude the renal arteries, the left earlier and the right later or terminally. There was no source for an embolus in the heart, although one cannot rule out the possibility of a mural thrombus in the left ventricle years previously, with subsequent embolization and superimposed thrombosis of the abdominal aorta.

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THE POSTGRADUATE MEDICAL INSTITUTE

ONE of the distinctions of being a physician is the necessity to be continually educated and re-educated in medicine. Although the ultimate responsibility of obtaining this education rests on the doctor himself, adequate opportunities must be made available to him. The problems inherent in the development of effective programs are numerous and complex and have not been adequately attacked. They deserve the attention of the best brains in the field of medical education and generous financial support.

The ultimate concern of the Massachusetts Medical Society is the provision of good medicine to the public everywhere throughout the State. Whatever socioeconomic adjustments in medical practice may come, and whatever the solution to the number of physicians practicing may be, it is clear that the quality of medical service furnished is as important as the quantity. Such quality cannot be maintained without the provision of opportunities for continuing education of physicians.

Postgraduate medical education has long been the concern of the Massachusetts Medical Society. Indeed, the Society has been in the forefront of state medical societies in this respect, as the Sanders Theatre and Boston Medical Library Lecture courses, the New England Postgraduate Medical Assembly, the Amherst Conference and the lecture series in the various districts attest. Last year the Committee on Postgraduate Medical Education took another significant step forward by bringing together representatives of all the medical schools in this state, the Harvard School of Public Health and the Joslin and Lahey clinics to explore the possibility of a co-operative effort in furnishing medical teaching. With the support of these groups and many of the voluntary health agencies, as well as that supplied by the Society, the effort was launched as the Survey of Postgraduate Medical Education. A clearing house of medical information has been set up at 22 Fenway, and progress has already been made in developing teaching programs in community hospitals. Plans for presenting formal courses are underway.

The Committee on Postgraduate Medical Education has decided that this collaborative effort should be continued on a permanent basis and has recommended that the name of the Survey be changed to the Postgraduate Medical Institute as more appropriate to its functions. The Council will be asked to approve this recommendation at its next meeting. It is indeed challenging to speculate about what may develop from this organization, launched by and intimately connected with the Massachusetts Medical Society but drawing into its fold the co-operative efforts of the schools, hospitals and other groups that, together, make Boston one of the great medical centers in the world.

THAT THE BLIND MIGHT READ

Louis Braille, the son of a French saddler, died of tuberculosis on January 6, 1852, at the age of forty-three. Deprived of his sight when he was three years old, the result of an accident sustained while he was playing with his father's awl, he developed and published, when he was but twenty years of age, the best known and the most useful system of printing that has yet been devised for the fingers of the blind to read.

Although during the nineteenth century alone twenty-three methods of embossed printing for the blind were in existence, it was the Braille system that came into common use, being "translated" even into Chinese. Of the other systems the best known are Lucas's, Frere's and Moon's. The Moon system, also in current use, partly retains the roman outlines and is best adapted for those who become blind late in life.

Other devices by which the blind may retain contact with recorded throught and even with the manipulation of figures have been invented. Taylor's arithmetic board, with star-shaped openings designed to take a square pin in eight positions, can be employed in the solution of complicated problems in both arithmetic and algebra.

The name of Braille stands pre-eminent above the others, however. His contribution in a short life that ended a century ago was truly to make the world's literature available to the sightless.

A LONDON LETTER

The most important fact in the world in his time, according to Germany's Iron Chancellor, was that the American people spoke the English language. The Marquess of Reading, addressing the orthopedic congress held recently in London, has suggested that the most important thing today might rather be that the English people speak American. Regardless of which way the linguistic tide happens to be running at the moment — East or West — one of the present stabilizing influences in the world is that the people of the British Commonwealth and those of the United States do speak and understand a common language and in many ways think along the same lines.

In view of this common denominator it has seemed a fortunate circumstance to the editors of the *Journal* that a London "correspondent" has been found who is willing to present from time to time an account of matters of general medical interest in Great Britain. Our reporter, whose first installment of "By the London Post" appears elsewhere in this issue of the *Journal*, is John Lister, M.D., M.R.C.P., of the Royal Free Hospital in London, a young clinician and former editor. Dr. Lister has already demonstrated his versatility in both English and American.

STREAMLINING THE LITTLE RED SCHOOLHOUSE FOR PRACTITIONERS

The Postgraduate Medical Institute, whose birth is described above, has lost no time in offering something to the practitioners of this state. It announces a course in general medicine to be given from 3 to 5 p.m. on Wednesdays from October, 1952, to April, 1953. The sessions will be down-to-earth clinical presentations aimed at the physician who is caring for patients in his office, the home and in community hospitals not as well supplied with elaborate appurtenances as some of the teaching hospitals.

The program will be carefully planned, and the teaching carried out by a co-operative group drawn from the various medical schools, the Harvard School of Public Health, the Joslin and Lahey clinics and other agencies concerned with medical teaching. The ultimate consumer, the practicing physician, will not be forgotten in the planning, for representatives of such practitioners will be consulted, including the Academy of General Practice. With such a group behind this course, fine fare indeed should be furnished, and practitioners had better sign up promptly, for the attendance will be limited. This course will supplant the lecture series that has been given annually with such success at the Boston Medical Library.

A fee will be charged for the course, as is customary in postgraduate courses sponsored by most state medical societies. The proper establishment and expansion of a program of postgraduate education is an expensive proposition. Although the Society as a whole furnishes significant support to this

endeavor, it is proper that the major cost be borne by the particular beneficiaries, the physicians who subscribe to the course. Spread in this way, the cost will be small indeed for such an educational feast — only $1.00 per hour of teaching. Moreover, doctors, like all other human beings, appreciate that which they have to pay something for more than they do a free handout, the hallmark of the welfare state.

The Postgraduate Medical Institute has not forgotten the doctors who live at a distance from Boston. It is its intention to offer similar courses — properly adapted and modified to local needs — in areas throughout the Commonwealth. First, however, there must be evidence that there is enough local interest and initiative to warrant this teaching. The Institute stands ready to give its help anywhere in the State, but it is not going to dictate to local groups what they want or need.

In alluding to Mr. Miller's importation of the newly invented India Rubber Stocking, so useful in protecting a varicose limb, we inadvertently called it laced *instead of* elastic. *However, this gives us additional opportunity to confirm the statement that it is an important invention.*

Boston M. & S. J., *September 8, 1852*

BY THE LONDON POST

CONFERENCE TIME

ALTHOUGH it is the impression of many Americans that there are fewer medical meetings in Britain than in the United States, this impression is scarcely borne out now, at the height of the present conference season.

For the fourth time in a hundred and twenty years the British Medical Association has been holding a joint annual meeting with the Irish Medical Association in Dublin. The President (Dr. P. T. O'Farrell) in his opening address recalled that it was at the first Dublin meeting in 1867 that Joseph Lister delivered his famous address "On the Antiseptic Principle of the Practice of Surgery." He pointed out that since that time great advances and great changes have taken place in medicine. Today the attention of the world is focused on the influence of the Welfare State with its socialized medicine upon the practice of our profession. A new relation has developed between the doctor and the State, the most serious result of which seems to have been an alteration of the status of the general practitioner. His position as friend, counsellor and confidant has declined in the eyes of the public. The President suggested, however, that all blame could not be attached to the State. The profession on its part should try to halt the tendency to overspecialization, and great efforts should be made to raise the standard of general practice. More students should be encouraged to aim at general practice as their goal. To that end he suggested that general practitioners might be appointed to the staffs of teaching schools so that students might receive some undergraduate instruction in this field. He believed that the general practitioner should occupy a position second to none in the profession and pointed out that he can practice the true Hippocratic approach to medicine with much more sympathy than can the specialist, whose work confines him to a narrower field — "Where there is love of humanity, there too is love of the art."

The opening days of the meeting were devoted to business and matters of general principle. Dissatisfaction with the scales of remuneration of general practitioners has been one of the main causes of discontent amongst doctors in the National Health Service. Their case has largely been met by the award of £40,000,000 on the recent hearing by Judge Danckwerts, and delegates received with appreciation a report of how their case had been prepared. The sum will be distributed amongst practitioners to cover what is considered by Judge Danckwerts to be underpayment for services rendered since the inception of the Health Service in 1948. Furthermore, a working party composed of members of the Government and of the B.M.A. has reached agreement on future scales of pay, which should do much to remove remaining grievances.

An interesting matter of principle was raised when it was suggested by the Central Ethical Council (of the B.M.A.) "that in general it is a practitioner's obligation to observe strictly the rule of professional secrecy but that there will doubtless occur certain special occasions when it may become a doctor's moral or social duty for the protection of innocent persons to make disclosures to an interested party." Many speakers cited the case of epileptics who insiste on driving motor cars or trucks, and one pleaded that now that epileptics have become mechanized they are lethal and it is the doctor's duty to protect the public against them — if necessary by disclosing the nature

of their illness to a third party. In spite of such dramatic representations the meeting would not countenance any deviation from that part of the Hippocratic Oath which says "Whatsoever things I see or hear concerning the life of men in my attendance on the sick or even apart therefrom, which ought not to be noised abroad, I will keep silence thereon, counting such things to be as sacred secrets."

The meeting did, however, pass an important resolution stating, "That this meeting deplores the complacent attitude of the Ministry of Health with regard to the adequacy of its propaganda in infectious diseases, especially with regard to vaccination." Compulsory vaccination was abolished in 1948, and in some parts of the country the vaccination rate for infants has fallen below 50 per cent. Propaganda in favor of vaccination, which is limited to visits from a health visitor and advice at infant welfare centers, has to compete with literature of antivivisection societies distributed by post.

During the second week, to offset a somewhat intensive program of political and professional thought, a number of social functions including a garden party at Trinity College and a state reception for overseas and foreign delegates were held. According to tradition, too, there were both Protestant and Roman Catholic church services where members attended in full academic dress. Finally, there was a hobbies exhibition, which, the President explained, had probably been revived because many Britons think as some of our American friends do that "a hobby is something you go goofy over to keep you from going nuts over things in general!" There were about 200 exhibits, including handwoven clothes, a set of powder puffs, boats and collections of books, giving some indication of how nationalized British doctors spend their leisure.

In addition to the B.M.A. meeting there have been a number of international conferences of note. First, the Orthopaedic Associations of the English Speaking World held a joint meeting in London from June 30 to July 4. The Congress was opened by Her Majesty Queen Elizabeth the Queen Mother, who presented jewels of office to the presidents of the visiting associations of Australia, Canada, New Zealand, the United States and South Africa.

Speakers at the scientific meetings included members of all the participating associations. Dr. William A. Rogers (Boston), among other speakers, reported his results in a series of cases of fracture dislocation of the cervical spine.

At the congress dinner, the final toast was to the English language. The importance of co-operation between the English-speaking peoples was stressed by the proposer, the Marquess of Reading. He quoted Bismarck's saying that the most important thing is that the American people speak English and suggested that today he might have said that the most important thing is that the English people speak American! Lord Justice Birkett, responding said that the English tongue is one of the bonds between the nations that use it, and in such bonds, he believed, lies the chief hope of the world.

Also in London during the current season there is an International Congress of Physical Medicine under the chairmanship of Lord Horder, and the International Diabetes Federation held its first Congress in Leyden, Holland, July 7–12. At this congress the President was Dr. C. H. Best, and the many distinguished personalities who were present included Dr. Elliott P. Joslin, Dr. H. C. Hagedorn and Dr. R. D. Lawrence. Many of those attending this congress were remaining in Holland for another week to attend a UNESCO Conference, and others were later going to Paris for the Biochemistry Congress.

JOHN LISTER

London

BOSTON MEDICAL LIBRARY

NOTES

The Medizinal-Kalender, formerly Börner's calendar, has survived for seventy-three years. It is now published by Georg Thieme, of Stuttgart. There is a long list of approved drugs, a kind of pharmacopeia, and a valuable list of proprietary remedies compiled to July, 1951. The description of each remedy notes its chemical formula, use, price and manufacturer. Much other valuable material is contained in the small volume.

As bases anatomo-patológicas da neuriatria e psiquiatria, in 2 volumes (São Paulo, 1951), by Walter Maffei, is an excellent treatise on the pathological anatomy of the nervous system, including psychiatric conditions affecting the brain. The material is systematically arranged, dealing in order with anomalies, degenerative processes, circulatory disturbances, inflammations, syphilis, tumors and parasites of the nervous system, pathology of the meninges and nerves and traumatism. The work is profusely illustrated with fine cuts reproduced from sections. The type and printing are excellent. The language is Portuguese, but simple in character. A person familiar with Spanish should be able to comprehend the essence of the text.

Bernhard Steinberg's *It Was My Idea* (Chicago, 1951), an amusing set of cartoons depicting the trials and tribulations of the research worker, is published by courtesy of the Armour Laboratories. Dr. Steinberg is director of the Toledo Hospital Institute of Medical Research.

Through the courtesy of Mr. Joseph Shields, consul of Ireland in Boston, the Library has received a copy of the recent book written by John Fleetwood, M.B., entitled *History of Medicine in Ireland* (Dublin, September, 1951).

The history covers the whole period from the pre-Christian era and the Brehon laws to the twentieth century. The laws were first promulgated several hundred years before the birth of Christ. There are chapters on Trinity College, Dublin, founded in 1591, the Royal College of Physicians, founded in 1626, and the Royal College of Surgeons, founded in 1784. Chapters are devoted to the Dublin School of Midwifery, founded in 1745, and the history of obstetrics in Ireland, and the book also discusses hospitals and medical schools.

Throughout the text, there are short biographies of eminent Irish physicians and surgeons, with lists of their important publications. One notes such important names as Abraham Colles (Colles fracture), John Cheyne (Cheyne–Stokes respiration), William Stokes, (diseases of the chest), Robert Graves (exophthalmic goiter) and Richard Quain (surgery).

There are valuable chapters on professional societies and publications. An appendix presents a chronology of historical events relating to Irish medical history. There is a bibliography of sixteen pages and an excellent index. The text is written in a pleasing, narrative form.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

LABORATORIES APPROVED FOR DIAGNOSTIC SEROLOGIC TESTS FOR SYPHILIS

On the basis of the evaluation of serologic tests for syphilis for 1951–1952, the 39 laboratories that have been granted approval for diagnostic tests to August 8, 1953, are listed below. Only laboratories approved by the Department of Public Health for diagnostic serologic tests for syphilis may legally perform the *premarital* and *prenatal* blood tests required by law. The Wassermann Laboratory, at 281 South Street, Jamaica Plain, is the only laboratory in Massachusetts whose reports for premarital purposes are recognized in other states.

Location	Laboratory
Boston	Boston Dispensary
	Boston Health Department
	Commonwealth Clinical Laboratory
	Leary Laboratory
	Massachusetts General Hospital
	Massachusetts Memorial Hospitals, Genito-Infectious Disease Clinic
Brockton	Board of Health Laboratory
Brookline	Sias Laboratories
Cambridge	Mount Auburn Hospital
Clinton	Clinton Hospital
Fall River	St. Anne's Hospital
	Union Hospital
Fitchburg	Burbank Hospital
Great Barrington	Fairview Hospital
Greenfield	Franklin County Public Hospital
Haverhill	Hale Hospital
Holyoke	Holyoke Hospital
	Providence Hospital
Lawrence	Lawrence General Hospital
Lowell	Lowell General Hospital
Montague	Farren Memorial Hospital
New Bedford	Burt Clinical Laboratory
	St. Luke's Hospital
Newton	Newton–Wellesley Hospital
North Adams	North Adams Hospital
Norwood	Norwood Clinical Laboratory
Pittsfield	Hillcrest Hospital
	Pittsfield General Hospital
	St. Luke's Hospital
Quincy	Quincy City Hospital
Salem	Salem Hospital
Springfield	Mercy Hospital
	Springfield Hospital
Tewksbury	Tewksbury State Hospital and Infirmary
Waltham	Waltham Hospital
Worcester	Department of Public Health Laboratory
	St. Vincent Hospital
	Worcester City Hospital
	Worcester Hahnemann Hospital

SURVEY OF PHYSICIANS AND ALLIED PERSONNEL

A survey of physicians and allied medical personnel will be undertaken by the Massachusetts Civil Defense Agency, Medical and Health Division, September 22 to 27, inclusive.

The purpose of this survey is to make available information regarding the number and location of many categories of medical personnel, which is of vital importance for civil-defense planning. The information obtained will be used by the Medical and Health Division of the Massachusetts Civil Defense Agency in its plans to cope with any disaster that may befall the Commonwealth, whether civilian or the result of enemy action. Such information will also be utilized in the planning and staffing of improvised hospitals and first-aid stations, which will have to be established to cope with

any large number of casualties such as would result from an atomic-bomb disaster.

The Massachusetts Hospital Association and the Massachusetts Retail Druggist Association have indicated a willingness to assist in the survey through local hospitals and drugstores. Therefore, registration cards will be available at all hospitals and in many drugstores in the Commonwealth during the period of the survey.

It is hoped that every physician in the Commonwealth will co-operate in having a card completed either at a hospital or at his local drugstore.

SEVEN DAYS' ISOLATION FOR POLIOMYELITIS

The communicable-disease regulations of the Massachusetts Department of Public Health were recently amended to change the period of isolation of patients with poliomyelitis from fourteen to seven days after onset. This change is being made because such a period of isolation is becoming standard throughout the country. Many states have already taken this action. The change in the regulations became effective on August 12, 1952.

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR JULY, 1952

RÉSUMÉ

DISEASE	JULY 1952	JULY 1951	SEVEN-YEAR MEDIAN
Chancroid	0	1	2
Chicken pox	419	438	490
Diphtheria	0	2	14
Dog bite	1404	1382	1333
Dysentery, bacillary	0	10	9
German measles	557	202	114
Gonorrhea	126	213	284
Granuloma inguinale	1	1	0
Lymphogranuloma venereum	0	0	0
Malaria	12	20	15
Measles	611	1202	1162
Meningitis, meningococcal	5	6	5
Meningitis, Pfeiffer bacillus	3	4	2
Meningitis, pneumococcal	1	0	2
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	6	5	3
Mumps	233	784	442
Poliomyelitis	31	64	21
Salmonellosis	12	7	7
Scarlet fever	46	119	125
Syphilis	172	139	216
Tuberculosis, pulmonary	239	184	243
Tuberculosis, other forms	15	19	13
Typhoid fever	1	3	3
Undulant fever	3	0	4
Whooping cough	107	110	432

COMMENT

Diseases that exceeded the seven-year median included German measles, poliomyelitis and salmonellosis.

With the exception of 1935, the incidence of German measles was the highest for July since 1917, when it was first reported.

The 31 cases of poliomyelitis, although higher than the seven-year median, were less than half those of July, 1951.

Diseases below the seven-year median included diphtheria, measles, mumps, scarlet fever and whooping cough. (There has never previously been a month in which no cases of diphtheria were reported.)

The incidence of measles reported was exceptionally low, only three years, 1949, 1935 and 1919, being lower since 1907.

The incidence of mumps was the lowest since 1946.

Scarlet fever and whooping cough were both at the lowest point since reporting began in 1906 and 1915 respectively.

GEOGRAPHICAL DISTRIBUTION OF CERTAIN DISEASES

The following diseases were reported from the communities named:

Anthrax was reported from: Chelmsford, 1.

Encephalitis, infectious was reported from: Plymouth, 1; Sharon, 1; Uxbridge, 1; total 3.

Hepatitis, infectious was reported from: Boston, 2; Bourne, 1; Leicester, 1; Lowell, 1; Sutton, 1; Worcester, 5; total 11.

Malaria was reported from: Camp Edwards, 4; Fort Devens, 8; total 12.

Meningitis, meningococcal was reported from: Boston, 1; Chicopee, 1; Fall River, 1; Waltham, 1; Worcester, 1; total 5.

Meningitis, Pfeiffer bacillus was reported from: North Adams, 1; Pittsfield, 1; Springfield, 1; total 3.

Meningitis, pneumococcal was reported from: Boston, 1; total 1.

Meningitis, undetermined was reported from: Boston, 1; Falmouth, 1; Hanson, 1; Holyoke, 1; Pittsfield, 1; Worcester, 1; total 6.

Poliomyelitis was reported from: Boston, 3; Brookline, 1; Cambridge, 1; Lincoln, 1; Lowell, 1; Lynn, 9; Malden, 4; Marblehead, 1; Methuen, 1; Nahant, 1; Northbridge, 1; Scituate, 1; Sharon, 1; Somerville, 1; Springfield, 1; Swampscott, 1; Watertown, 1; Worcester, 1; total 31.

Salmonellosis was reported from: Boston, 1; Brookline, 1; Holyoke, 1; Lynn, 1; Melrose, 6; Saugus, 1; Wakefield, 1; total 12.

Septic sore throat was reported from: Boston, 2; Brewster, 1; Easthampton, 1; Quincy, 2; total 6.

Trichinosis was reported from: Boston, 2; Malden, 1; total 3.

Typhoid fever was reported from: Andover, 1.

Undulant fever was reported from: Chicopee, 1; Reading, 1; Worcester, 1; total 3.

BOOK REVIEWS

Manic-Depressive Psychosis and Allied Conditions. By Leopold Bellak, M.D., with Blaise Pasquarelli, M.D., Ernest Parkes, M.A., and Sonya S. Bellak, and the collaboration of Sydell Braverman, M.A. With a foreword by Winfred Overholser, M.D. 8°, cloth, 306 pp., with 21 illustrations. New York: Grune and Stratton, 1952. $9.75.

This volume represents an impressive compilation of the numerous factors associated with the manic-depressive psychosis. As in his work on dementia praecox, the author has painstakingly examined the greater portion of the worthwhile literature and has arranged the material in a well organized manner. He treats the subject from every point of view, considering the various etiologic aspects, the psychodynamics and psychopathology, and treatment in general.

In summary, this is an extremely valuable text of present knowledge on manic-depressive psychosis and, as such, is worth while from the point of view of the student, who will find a complete survey, and from the point of view of the more advanced reader, for whom it will be an easy source of reference. In addition, Dr. Bellak presents his own interesting, invaluable point of view.

HUBERT A. CARBONE, M.D.

Visceral Innervation and Its Relation to Personality. By Albert Kuntz, M. D., Ph.D. 8°, cloth, 152 pp., with 31 illustrations. Springfield, Illinois: Charles C Thomas, 1951. $4.50. (Publication No. 115, American Lecture Series.)

In this short volume the author correlates the neuroanatomic structure and the physiologic mechanisms of the central nervous system with the aspects of the personality that are directly associated with visceral and somatic responses subserved by the autonomic nervous system. The discussion on neuroanatomy and neurophysiology is well integrated, concise and clear, synthesizing much of the known knowledge of the subject. The author attempts to draw a parallel between types of personality and predominance of one or the other components of the autonomic nervous system.

In short, this volume is an excellent summary of the relation between the autonomic nervous system and the visceral responses associated with various emotional reactions.

HUBERT A. CARBONE, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Clinical Pediatric Urology. By Meredith Campbell, M.D., professor of urology, New York University Post-Graduate Medical School, and visiting urologist, Bellevue and University Hospitals, New York. With a section on *Nephritis and Allied Diseases in Infancy and Childhood* by Elvira Goettsch, M.D., associate professor of pediatrics, University of Southern California School of Medicine, and assistant medical director of the Children's Hospital Society of Los Angeles, and John D. Lyttle, M.D., medical director of the Children's Hospital Society of Los Angeles. 8°, cloth, 1113 pp., with 543 illustrations. Philadelphia: W. B. Saunders Company, 1951. $18.00.

Clinical Urography: An atlas and textbook of roentgenologic diagnosis. By William F. Braasch, M.D., and John L. Emmett, M.D., consultant in urology, Mayo Clinic, and associate professor of urology, Mayo Foundation, Graduate School, University of Minnesota. 4°, cloth, 736 pp., with 1361 illustrations. Philadelphia: W. B. Saunders Company, 1951. $25.00.

Renal Function: Transactions of the Second Conference, October 19-20, 1950, New York. Edited by Stanley E. Bradley, M.D., Department of Medicine, Columbia University College of Physicians and Surgeons. 8°, cloth, 178 pp., with 31 illustrations. New York: Josiah Macy, Jr., Foundation, 1951. $3.00.

Conference on Problems of Aging: Transactions of the Thirteenth Conference, February 5-6, 1951, New York. Edited by Nathan W. Shock, M.D., chief, Section on Gerontology, National Heart Institute, National Institutes of Health and the Baltimore City Hospitals. 8°, cloth, 194 pp., with 24 illustrations. New York: Josiah Macy, Jr., Foundation, 1951. $4.00.

Nerve Impulse: Transactions of the Second Conference, March 1-2, 1951, New York, New York. Edited by David Nachmansohn, M.D., Department of Neurology, Columbia University College of Physicians and Surgeons. 8°, cloth, 204 pp., with 37 illustrations. New York: Josiah Macy, Jr., Foundation, 1951. $3.50.

Metabolic Interrelations: Transactions of the Third Conference, January 8-9, 1951, New York. Edited by Edward C. Reifenstein, Jr., M.D., Oklahoma Medical Research Institute and Hospital, Oklahoma City. 8°, cloth, 294 pp., with 85 illustrations. New York: Josiah Macy, Jr., Foundation, 1951. $4.00.

Liver Injury: Transactions of the Ninth Conference, April 27 and 28, 1951, New York. Edited by F. W. Hoffbauer, M.D., Department of Medicine, University of Minnesota Medical School. 8°, cloth, 232 pp., with illustrations and tables. New York: Josiah Macy, Jr., Foundation, 1951. $3.00.

Factors Regulating Blood Pressure: Transactions of the Fifth Conference, February 15 and 16, 1951, New York. Edited by Benjamin W. Zweifach, M.D., and Ephraim Shorr, M.D., Department of Medicine, Cornell University Medical College. 8°, cloth, 238 pp., with 49 illustrations and 24 tables. New York: Josiah Macy, Jr., Foundation, 1951. $3.75.

International Pharmacopoeia. First edition. Volume I. 8°, cloth, 406 pp. Geneva: World Health Organization, 1951. 35.— $5.00 Sw. fr. 20.— Bulletin of the World Health Organization. Supplement 2.

This new pharmacopeia strives to unify internationally the terminology, the strengths and the composition of pharmaceutical preparations. The book is divided into two parts: first, the recognized standard substances, and secondly, various appendixes of reagents, test solutions, assays, doses and so forth. There is a good index and the publishing is excellent. The book should be in all collections on pharmacology and pharmacy.

Surgery of Peripheral Nerves. By Emil Seletz, M.D., assistant clinical professor of neurological surgery, University of Southern California School of Medicine, associate senior attending neurosurgeon, Cedars of Lebanon Hospital, and junior attending neurosurgeon, Los Angeles General Hospital. 4°, cloth, 185 pp., with 136 illustrations. Springfield, Illinois: Charles C Thomas, 1951. $10.75.

This atlas is based on the author's personal experience with 2037 cases of peripheral nerve injuries. The new and original variations in technic developed by the author and his associates are described; the fortunate results obtained are attributed in part to the new methods. The fine plates are reproduced from drawings made in the operating room. The book should be in all collections on neurosurgery.

Conference on Viruses as Causative Agents in Cancer: Friday, November 16, and Saturday, November 17, 1951 (under the sponsorship of the New York Academy of Sciences, Section of Biology). 4°, paper, 46 pp. New York: New York Academy of Sciences, 1951.

This long news release presents substantial abstracts of the important papers read at the conference. The material is divided into three categories: virus-cell relations, host resistance to virus infections and tumor-producing viruses. The release will provide information in advance of the printed transactions.

The New Way to Better Hearing Through Hearing Re-education. By Victor L. Browd, M.D., adjunct professor of otolaryngology, New York Polyclinic School and Hospital. With an introduction by Robert West, Ph.D., head of Speech Clinic, Brooklyn College. 8°, cloth, 226 pp. New York: Crown Publishers, Inc., 1951. $3.00.

Dr. Browd describes his method of improving impaired hearing without the use of surgery, drugs or mechanical aids.

NOTICES

NEW HAMPSHIRE AND VERMONT STATE MEDICAL SOCIETIES

The third annual combined meeting of the New Hampshire and Vermont State Medical Societies, including the Woman's Auxiliaries, will be held at the Mount Washington Hotel, Bretton Woods, New Hampshire, September 7-9.

In addition to meetings of the respective Houses of Delegates, the program includes scientific sessions, a sports dinner, motion pictures, dancing, a "Dutch treat" cocktail party and the annual banquet. Dr. Louis H. Bauer, president of the American Medical Association, will be one of the guest speakers.

SOCIETY MEETINGS AND CONFERENCES

SEPTEMBER 7–9. Combined session of the New Hampshire and Vermont State Medical Societies. Notice above.

SEPTEMBER 8–20. First Argentine Congress of Thoracic Surgery. Page 1024, issue of June 26.

SEPTEMBER 9. Springfield Academy of Medicine. Speaker, Dr. W. B. Sherman, New York City.

SEPTEMBER 17. Phi Delta Epsilon Lecture. Page 338, issue of August 28.

SEPTEMBER 19. Combined Anesthesia Teaching Conferences of Boston. Page 304, issue of August 21.

(*Notices concluded on page xv*)